

STUDIES CONCERNING STEREOSELECTIVE,
REGIOSELECTIVE AND CATALYTIC ORGANOMETALLIC
REAGENTS IN ORGANIC SYNTHESIS

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STUDIES CONCERNING STEREOSELECTIVE,
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REAGENTS IN ORGANIC SYNTHESIS

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The author would like to dedicate this thesis to his mother, Vera E. Noding Langfeldt, and in loving memory to his father, Alfred L. Noding, who provided him with the opportunity and incentive to attend high school and college. Any success the author has or will have is based upon the inspiration and foundation they laid.

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SUMMARY

PART I. A STUDY OF STERIC APPROACH CONTROL

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PRODUCT DEVELOPMENT CONTROL

The concept of "product development control" has been used to explain the stereochemistry of many reactions in which the observed isomer ratio reflects the stability of the product. This concept has been used particularly to explain predominant formation of the most stable isomer in reactions of LiAlH_4 and MeMgBr with substituted cyclohexanones. A study of the reaction of LiAlH_4 and MeMgBr with 7-norbornanone and its exo-2-methyl and endo-2-methyl derivatives shows that the most unstable isomer is formed exclusively and hence "product development control" is not a factor in these reactions. In an attempt to broaden the scope of this study, three series of reagents were studied: (1) LiBH_4 , LiAlH_4 and LiGaH_4 , (2) BH_3 , AlH_3 and GaH_3 , and (3) $(\text{CH}_3)_2\text{Be}$, $(\text{CH}_3)_2\text{Zn}$, $(\text{CH}_3)_2\text{Mg}$ and $(\text{CH}_3)_3\text{Al}$. In no case was "product development control" observed. The reactions with the 7-norbornanone system are similar in nature to those with cyclohexanones, except that the complicating factors of torsional strain, compression effects and conformational changes which are present in cyclohexanone systems are not present in the 7-norbornanone system. The concept of "product development control" is, therefore, a questionable one in ketone reductions involving LiAlH_4 and alkylations involving MeMgBr .

PART II. HYDROMETALLATION OF ALKENES AND ALKYNES

CATALYZED BY TRANSITION METAL HALIDES

We have found that bis-dialkylaminoalanes, $\text{HAL}(\text{NR}_2)_2$, when allowed to react with alkenes or alkynes in the presence of a catalytic amount of Cp_2TiCl_2 provide high yields of deuterated or iodinated hydrocarbons when the reaction mixtures are quenched with D_2O or a benzene solution of iodine. These hydrometallated species were also allowed to react with carbonyl compounds (e.g. benzaldehyde); however, the normal addition products were produced in very low yields. Instead, associated tertiary amines (PhCH_2NR_2) were produced in substantial amounts. Our investigations also included other catalytic hydrometallation reactions of alkenes and alkynes with simple and complex metal hydrides. By using Cp_2TiCl_2 as a catalyst with LiAlH_4 , NaAlH_4 , Vitride, $\text{LiAl}(\text{NEt}_2)_2\text{H}_2$ and $\text{NaAl}(\text{NEt}_2)_2\text{H}_2$, $\text{NaAl}(\text{NEt}_2)_2\text{H}_2$, quantitative yields of deuterated products were obtained which in some cases were a distinct improvement over previous literature reports. Stoichiometric reactions of LiH-VCl_3 with ketones, aldehydes or enones were also investigated. Similar reactions with alkynes did not take place; however, with alkenes, the reactions produced alkanes although only a small amount of deuterium incorporation was observed when the reaction was quenched with D_2O .

A stereochemical study involving the reduction of cyclic ketones with $\text{HCo}(\text{CO})_4$ was also undertaken. Unfortunately, the reactions were so slow that only small amounts of the corresponding alcohols (equal ratios of axial and equatorial alcohols) were produced.

A preliminary investigation of carbonylation of simple and complex metal hydrides in the presence of transition metal halide catalysts was also conducted. During this study no alcohol or formate products were observed.

PART III. REACTIONS OF MAGNESIUM HYDRIDE:

STEREOSELECTIVE REDUCTION OF CYCLIC AND BICYCLIC KETONES BY LITHIUM ALKOXYMAGNESIUM HYDRIDES

A series of lithium alkoxymagnesium hydrides, $\text{LiMgH}_2(\text{OR})$, were prepared and allowed to reduce 4-t-butylcyclohexanone (I), 3,3,5-trimethylcyclohexanone (II), 2-methylcyclohexanone (III) and camphor (IV). It was found that very bulky secondary cyclic alkoxy groups such as 2,2,6,6-tetramethyl- or benzylcyclohexoxy were very stereoselective in the reduction of these ketones. For example, $\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_4\text{C(CH}_3)_3)$ reduced ketone (I) to provide 89% of the axial alcohol compared to $\text{HMgO}-\text{C}_6\text{H}_4\text{C(CH}_3)_3$ which provided 83% of the axial alcohol.

The $\text{LiMgH}(\text{OR})_2$ when $\text{R} = \text{C}_6\text{H}_4\text{C(CH}_3)_3$ or $\text{C}_6\text{H}_4\text{C(CH}_3)_3$ reagents were also found to reduce ketones (I), (II), (III) and (IV) stereoselectively but to a lesser extent and with more enolization than observed for the $\text{LiMgH}_2(\text{OR})$ reagents.

PART IV : CONCERNING SALT EFFECTS ON THE STEREOSELECTIVITY OF
ORGANOMETALLIC COMPOUND ADDITION TO KETONES

The reaction of 4-t-butylcyclohexanone with methyllithium in the presence of LiClO_4 resulted in the formation of the corresponding axial alcohol in 92% yield. This was a very unusual stereochemical observation in that only 65% of the axial alcohol was formed in the absence of LiClO_4 . This result was attributed to complexation of the ketone by LiClO_4 followed by the addition of CH_3Li to the carbonyl group rather than by addition of a $\text{CH}_3\text{Li-LiClO}_4$ complex directly to the uncomplexed ketone. To complete a more detailed investigation of this unusual result, other salts and ketones were studied in a similar manner. In addition to CH_3Li , $(\text{CH}_3)_2\text{Mg}$ and $(\text{CH}_3)_3\text{Al}$ were also allowed to react with 4-t-butylcyclohexanone in the presence of equalmolar ratios of various salts were studied to exam the effect on the stereochemistry of the alcohol products.

It was shown that of all the salts tested, LiClO_4 had the greatest effect towards increased stereoselectivity of CH_3Li reagents. The other RLi reagents, t-butyllithium and phenyllithium, did not show as great an effect. Also, $(\text{CH}_3)_2\text{Mg}$ and $(\text{CH}_3)_3\text{Al}$ showed very little increased stereoselectivity when allowed to react with ketones in the presence of metal salts.

PART V: ALKYLATIONS OF ENONES AND KETONES USING
SUBSTITUTED ALKYLALUMINUM COMPOUNDS

Earlier workers in this group have shown that H_2AlI provided 100% of the 1,4-conjugate addition product when allowed to react with enones. The possibility of using R_nAlX_{3-n} compounds to promote the non-catalyzed 1,4-conjugate addition to enones under consistent conditions was studied. It was shown that for the enone reactions, the reagent which produced the greatest amount of 1,4-conjugate addition product without the presence of a catalyst was R_2AlI ; however, the yield was low.

A systematic study concerning these compounds towards the alkylation of model ketone systems in order to find an effective stereoselectivity reagent was also investigated. It was observed once again that the most stereoselectivity reagent was R_2AlI , but the reaction was extremely slow. Therefore, it can be concluded that the use of these reagents to effect 1,4-conjugate addition of enones or stereoselectivity addition to ketones is impractical.

PART I

A STUDY OF STERIC APPROACH CONTROL

VERSUS

PRODUCT DEVELOPMENT CONTROL

CHAPTER I

INTRODUCTION

Background

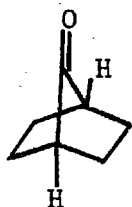
In recent years the area of stereoselective reduction and alkylation of ketones by metal hydrides and alkyls has received considerable attention.^{1,2} All mechanisms concerning the stereoselective addition or reduction of ketones assume that the entering group approaches the carbonyl carbon's π^* orbital on a plane perpendicular to the plane of the carbonyl group so that maximum orbital overlap is achieved in the transition state. Dauben and co-workers³ coined the terms "steric approach control" and "product development control" and suggested that these factors are important in determining the stereochemistry of LiAlH_4 reduction of cyclohexanones. "Steric approach control" implies an early, reactant-like transition state in which the entering group approaches the least hindered side of the ketone whereas "product development control" implies a late, product-like transition state in which the observed isomer ratio reflects the thermodynamic stability of the product.

The concept of "steric approach control" is generally agreed to be valid since certainly the ability of one molecule to approach another must depend to some extent on the steric requirements of the molecules involved. However, the concept of "product development control" has been questioned by Eliel and co-workers⁴⁻⁷ on the basis of competitive rate studies involving LiAlH_4 and 3,3,5-trimethylcyclohexanone. They have shown that an axial methyl group in the 3 and/or 5 position retards

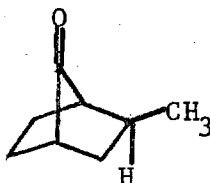
the rate of axial attack compared to 4-tert-butylcyclohexanone, whereas the rate of equatorial attack remains essentially the same. This observation is not consistent with that predicted by "product development control" in that an axial methyl substituent would be expected to retard equatorial attack.

As an alternative to "product development control", Cherest and Felkin introduced the concept of "torsional strain"⁸⁻¹¹ and we have developed the concept of "compression effect" to explain the unusual stereochemistry observed in the reactions of $(\text{CH}_3)_3\text{Al}$ with substituted cyclohexanones.¹² The cyclohexanone ring system may also undergo conformational changes, a factor which has been discussed by Landor and Regan.¹³ More recently orbital symmetry arguments¹⁴ and unequal distortion of electron density¹⁵ about the carbonyl group have been suggested to explain the stereochemistry of certain reactions.

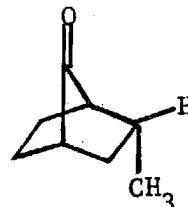
Alkylation and reduction studies of a model ketone system in which torsional strain, compression effects and conformation changes are not possible were carried out so that "steric approach control" and "product development control" could be evaluated independently of these other possible effects. 7-Norbornanone (I) exhibits bridgehead hydrogen atoms in the 1 and 4 positions which eclipse the carbonyl group in the 7 position. This unique feature, unlike that of the 2,6-diequatorial hydrogens in cyclohexanone which lie $4-5^\circ$ above the plane of the carbonyl group, eliminates torsional strain or compression effect as a complicating factor in evaluating stereochemical data obtained from this system. The fact that (I) is a rigid bicyclic system further eliminates conformational changes in the substrate as a further complicating factor. It



I



II



III

is clear then that the validity of the concept of "product development control" involving the reaction of LiAlH_4 or methyl magnesium bromide (Grignard reagents) as well as other reducing and alkylating reagents with ketones can be more rigorously tested using this system.

Purpose

In an attempt to broaden the scope of this study, three series of reagents were studied: (1) LiBH_4 , LiAlH_4 and LiGaH_4 , (2) BH_3 , AlH_3 and GaH_3 , and (3) $(\text{CH}_3)_2\text{Be}$, $(\text{CH}_3)_2\text{Zn}$, $(\text{CH}_3)_2\text{Mg}$ and $(\text{CH}_3)_3\text{Al}$. These reagents were allowed to react with 7-norbornanone (I), exo-2-methyl-7-norbornanone (II) and endo-2-methyl-7-norbornanone individually and competitively in order to evaluate the importance of "product development control" in the reduction and alkylation of ketones compared to "steric approach control".

CHAPTER II

EXPERIMENTAL

General Considerations

Manipulations of air-sensitive compounds were performed under nitrogen 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.¹⁶ Reactions were performed under nitrogen or argon at the bench using Schlenk tube techniques.¹⁷ Calibrated syringes equipped with stainless steel needles were used for transfer of reagents. Glassware and syringes were flamed or heated in an oven and cooled under a flow of nitrogen or argon. All standard solutions were prepared by weighing the solute in a tared volumetric flask and diluting with the appropriate solvent.

Materials

Fisher reagent grade anhydrous diethyl ether was distilled under nitrogen from LiAlH_4 prior to use. Fisher reagent grade tetrahydrofuran (THF) was distilled under nitrogen from NaAlH_4 prior to use. Hexachlorocyclopentadiene was obtained from Aldrich Chemical Company and used without further purification.

Lithium and sodium aluminum hydride solutions were prepared by refluxing LiAlH_4 (Alfa Inorganics) in THF or Et_2O and NaAlH_4 (Alfa Inorganics) in THF for at least 24 hours followed by filtration through a fritted glass funnel using dried Celite as a filter aid in the dry

box. The clear solution was standardized for aluminum content by EDTA.¹²

The same procedure was followed for LiBH_4 (Metal Hydrides).

Gallium chloride was purchased from Alfa Inorganics and used without further purification.

Borane in THF was purchased from Alfa Inorganics. Before using, the ratio of borane to hydride was checked.

The alkylating agents, Me_2Be , Me_2Zn and Me_2Mg were obtained from co-worker Dr. H. S. Prasad. Trimethylaluminum was obtained from the Ethyl Corporation. Before use, it was distilled under vacuum in the dry box.

Apparatus

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 spectrometer. The carbon-13 NMR spectra were obtained at 125 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. 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. Flame photometry was conducted on a Coleman Model 21 photometer.

Analytical

Gas analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Toepler pump.¹⁷ 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).¹⁸ Lithium was also determined by flame photometry. 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. Boron analyses were accomplished by the titration of boric acid-mannitol with standard NaOH.¹⁹ Carbon, hydrogen analyses were carried out by Atlantic Microlab, Inc., Atlanta, Georgia.

Preparations

Alane

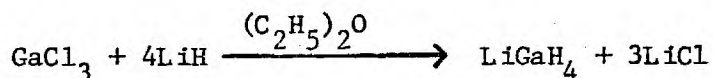
Alane (AlH_3) was prepared by the reaction of 100% H_2SO_4 with LiAlH_4 in THF at low temperature (dry ice-acetone temperature) and filtered in the dry box.²⁰ Analysis: Li:Al:H = 0.02:1.0:3.0.

Lithium Gallium Hydride

Lithium gallium hydride (LiGaH_4) was prepared according to a modification of a reaction reported in the literature.²¹ The apparatus used was a 1000 ml. three-necked ground glass joint round bottom flask. An equalizing pressure addition funnel was fixed to the flask. A rubber septum cap was fixed to the top of the addition funnel. One joint of the three-necked flask was plugged and a one-way valve was fastened to the other joint of the three-necked flask which in turn was connected to the

vacuum manifold and dry nitrogen so that an inert atmosphere of dry nitrogen was maintained.

In a typical synthesis 98.82g (0.56 mole) of gallium (III) chloride was dissolved in anhydrous diethyl ether. The flask was cooled with dry ice-acetone mixture because the dissolving of gallium (III) chloride in diethyl ether was very exothermic. A 100% excess of lithium hydride (36.64 g, 4.5 mole), obtained from Alfa Inorganics, and a stirring bar were placed in the three-necked round bottom flask under dry nitrogen after which 50 ml of anhydrous diethyl ether was syringed into the flask. The flask was cooled to -78°C under constant stirring. Next the gallium (III) chloride-ether solution was syringed into the addition funnel connected to the three-necked flask. The gallium (III) chloride-ether solution was added dropwise to the cold, stirred lithium hydride slurry. Slow addition of gallium chloride was important so that the solution did not heat up and cause thermal decomposition of the product (lithium gallium hydride). After the complete addition of gallium chloride-ether solution, the lithium gallium hydride solution was allowed to warm to 0°C . The solution was filtered and the precipitate washed with diethyl ether to maximize yield. The reaction for the procedure was:



The analysis²² showed a hydride to gallium ratio of 3.93 to 1.00 compared to the predicted 4.00 to 1.00 ratio. The per cent yield was estimated by comparing volumes of the ether solution and the volume of

water in a similar flask. Approximately 810 ml. of a 0.61 molar LiGaH_4 was produced. The per cent yield was 89%.

The solution was stored in a freezer under dry nitrogen. After 60 days no noticeable decomposition was observed. After this time the solution was reanalyzed and the hydride to gallium ratio was 4.00 to 1.00 and the concentration of gallium was 0.63 M. Lithium analysis was accomplished by flame photometry. The lithium: gallium: hydride ratio was 1.08 to 1.00 to 4.00. The solution was found to be chloride free after hydrolysis.

Gallane

Gallane (GaH_3) was prepared by the same procedure used to prepare alane. At -78°C , 100% H_2SO_4 was added slowly to the calculated volume of LiGaH_4 in Et_2O . After the desired time with stirring, the reaction mixture was allowed to warm to room temperature and filtered by the usual manner in the dry box. Analysis: $\text{Li:Ga:H} = 0.3:1.0:3.0$.

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (IV)

Hexachlorocyclopentadiene was converted to (IV) with methanolic potassium hydroxide according to a modified procedure by McBee.²³ In a 3-l. three-necked round bottom flask fitted with a condenser, an addition funnel, and a mechanical stirrer were placed 254 g (0.93 mole) of hexachlorocyclopentadiene and 800 ml. of commercial grade methanol. The stirrer was started, and a solution of 120 g (2.14 mole) of potassium hydroxide in 600 ml. of methanol added dropwise over a period of three hours. The reaction mixture was stirred for an additional two hours and then poured over 3 l. of crushed ice. After the ice had melted, the mixture was extracted with three 250-ml portions of dichloro-

methane. The combined extracts were dried over anhydrous magnesium sulfate and concentrated to a yellow syrup on a rotary evaporator. The residue after distilling through a 12 inch Vigreux column yielded 188 g. (76%) of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (IV) as a viscous, yellow-tinted oil, b.p. 79-82 °C (0.6 mm); NMR (CDCl_3 , TMS) singlet at 3.30 ppm; mass spectrum, m/e (rel. intensity) 237(M^+ -37, 2), 236(2), 235(4), 234(5), 233(3), 232(10), 231(2), 230(25), 229(10), 228(90), 227(15), 226(100), 225(3), 224(10), 206(3), 154(20), 58(30); IR (neat, film) 2970(m), 2940(s), 1610(s), 1450(s), 1190(s), 1140(s), 1100(m), 1080(m); n_D^{25} 1.5284 [lit.²³ b.p. 108-110 (11 mm), n_D^{25} 1.5288].

7,7-Dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene (V)

A 1-l. two-necked round bottom flask was fitted with a fritted-glass gas inlet tube and a condenser connected to a mercury filled bubbler. Into the flask was placed 188 g. (0.72 mole) of (IV), and a slow stream of nitrogen and ethylene was passed through the fritted-glass inlet tube at a rate to maintain about 1-2 inches of foam in the flask at 190° C which is heated by an oil bath. The color of the liquid changed from yellow to redish brown as ethylene was bubbled through the reaction mixture at this temperature for 6 hours. The reaction mixture was cooled and distilled through a 12-inch Vigreux column to yield 160 g. (75%) of a yellow syrup, b.p. 70-75 (0.15mm); NMR (CDCl_3 , TMS) 3H singlet at 3.50 ppm, 3H singlet at 3.55 ppm, 4H multiplet at 1.63-2.50 ppm; mass spectrum, m/e (rel. intensity) 265(M^+ -37, 10), 264(2), 263(4), 262(5), 261(4), 260(12), 259(4), 258(28), 257(9), 256(81), 255(15), 254(100), 253(7), 252(14), 234(5), 232(8), 230(9), 228(12), 226(16), 182(20), 180(23), 143(23), 142(18), 133(34), 58(40);

IR (neat, film) 2970(m), 2940(s), 2830(s), 1610(s), 1460(s), 1290(s), 1270(s), 1220(s), 1190(s), 1125(s), 1095(s), 1060(m), 1015(s), 995(s), 920(s), 875(s), 840(s), 800(s), 735(m); n_D^{25} 1.5250 [lit.²⁴ b.p. 56°C (0.05 mm), n_D^{25} 1.5248].

7,7-Dimethoxybicyclo[2.2.1]heptene (VI)

A 500 ml. three-necked round bottom flask was equipped with a mechanical stirrer, a condenser fitted with a nitrogen inlet tube to maintain a slight positive pressure, and a pressure-equalizing dropping funnel. The flask was placed in a heating mantle, and into it were placed 250 ml. of THF which had been distilled from NaAlH_4 , 23 g. (1 mole) of sodium metal chopped into 5-mm. cubes and 30 ml. (25 g., 0.33 mole) of t-butyl alcohol. This mixture was stirred vigorously and brought to gentle reflux. As soon as refluxing occurred, 17.7 g (0.06 mole) of (V) was added dropwise over a 2 hour period. The mixture was heated under reflux for 36 hours, cooled to room temperature and the excess sodium was destroyed by slow addition of 100 ml. methanol. The reaction mixture was poured over 2 l. of crushed ice and extracted with 200 ml. of diethyl ether. The aqueous phase was separated and the organic phase was washed with 3-250 ml. portions of saturated aqueous sodium chloride. The ethereal solution was dried over anhydrous magnesium sulfate and concentrated to a dark oil by removal of the ether by a rotary evaporator. The residue was distilled through a 12-inch Vigreux column to yield 6.1 g. (65%) of colorless liquid, b.p. 60-63°C (17 mm); IR (neat, film) 3060 (s), 2950 (s), 2820 (m), 1620 (s), 1190 (m), 1140 (m), 1105 (m), 1080 (m); NMR (CDCl_3 , TMS) 2H multiplet at 0.75-1.01 ppm, 2H multiplet at 1.63-2.01 ppm, 2H multiplet at 2.59-2.75 ppm, 3H singlet

at 3.05 ppm, 3H singlet at 3.13 ppm, 2H multiplet 5.90-6.07 ppm; mass spectrum, m/e (rel. intensity) 154(M^+ , 58), 139(18), 123(58), 107(22), 91(40), 79(100), 59(32); n_D^{25} 1.4645 [lit.²⁵ b.p. 74-78°C (30 mm); $n_D^{28.6}$ 1.4584].

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.19; H, 9.13.

This reaction proceeded smoothly when the listed quantities were used; however, when this reaction was scaled up 8 fold, a violent explosion ensued. Therefore caution should be exercised.

7,7-Dimethoxy[2.2.1]heptane (VII)

In a hydrogenation flask equipped with a magnetic stirrer, 6.1 g of (VI) and 0.03 g. of 5% palladium on carbon were stirred under hydrogen at room temperature and atmosphere pressure. After the hydrogen absorption had ceased, the catalyst was removed by filtration. The filtrate was vacuum distilled to give 5.5 g. (87%) of 7,7-dimethoxybicyclo[2.2.1]heptane, b.p. 78-80°C (30mm); NMR ($CDCl_3$, TMS) 10H multiplet at 0.83-2.04 ppm, 6H singlet at 3.18 ppm; IR (neat, film) 2980(s), 2960(s), 1450(s), 1195(m), 1130 (m), 1100(m), 1050(m); mass spectrum, m/e (rel. intensity) 156(M^+ , 100), 125(90), 111(33), 94(40), 83(88), 55(87); n_D^{25} 1.4530 [lit.²⁵ b.p. 80°C (30 mm); n_D^{25} 1.4533].

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.46; H, 10.28.

Bicyclo[2.2.1]heptan-7-one (I)

In a 25-ml. round bottom flask with distillation head, 2.06 g. (0.015 mole) of (VII) and 15 ml. (0.25 mole) of glacial acetic acid were heated to 115°C for 10 hours. After cooling, the solution was trans-

ferred to a separatory funnel with 30 ml. of petroleum ether (b.p. 35-45°C). A solution of 12 g. (0.30 mole) of sodium hydroxide in 40 ml. of water was carefully added dropwise with cooling. An additional 40 ml. of water was added to dissolve the sodium acetate that had formed. The water layer was separated and washed twice with 25-ml. portions of petroleum ether. The combined petroleum ether extracts were dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The filtrate was concentrated to 15 ml. The temperature was lowered to -20° to initiate crystallization. After crystallization was complete, the solvent was removed and the precipitate dried by passing nitrogen over the crystals to give 0.90 g. (62%) of bicyclo[2.2.1]heptan-7-one (I) [7-norbornanone], m.p. 77-79°C; IR (Nujol) 1845(w), 1760(s), 1740(w), 2920(s), 2840(s), 1460(s), 1380(m), 1300(m), 1200(m), 1180(w), 1160(m); NMR (CDCl₃, TMS) multiplet at 1.50-2.20 ppm; mass spectrum, m/e (rel. intensity) 110(M⁺, 80), 81(75), 67(95), 55(100); [lit.²⁵ m.p. 79.5-80.5°C; IR 1754(s), 1783(w)].

Anal. Calcd for C₇H₁₀O: C, 76.32; H, 9.15. Found: C, 76.40; H, 9.32.

Exo-7,7-dimethoxynorbornan-2-ol (VIII)

A 500-ml. round bottom flask equipped with a magnetic stirrer was charged with 12.76 g (0.04 mole) of mercuric acetate followed by 40 ml. of water. The mercuric acetate dissolved to give a clear solution. Tetrahydrofuran (40 ml) was added to the solution forming a bright yellow suspension. To the mixture, which was cooled in an ice bath, was added 0.038 mole of (VI) with stirring. The mixture was allowed to warm to room temperature with stirring until the reaction mixture became

colorless and clear (30 minutes). Stirring was continued for an additional 15 minutes and 40 ml. of 3 N sodium hydroxide was added followed by 40 ml. of 0.5 M sodium borohydride in 3 M sodium hydroxide. The reduction was almost instantaneous. The mercury was then allowed to settle and the water layer saturated with sodium chloride. The tetrahydrofuran layer was separated, dried with anhydrous sodium sulfate and filtered after which the solvent was removed by rotary evaporation. The crude product was distilled to give 0.030 mole, (5.2 g., 80%), of (VIII) b.p. 88-91°C (6-7mm); n_D^{26} 1.4372; IR(neat, film) 3600-3200(broad-s) 2950(s), 1170(m), 1145(m), 1115(m), 1060(m); NMR (CDCl₃, TMS) 6H multiplet at 0.88-2.17 ppm, 1H broad singlet at 2.92 ppm, 1H multiplet at 3.10 ppm, 3H singlet at 3.18 ppm, 3H singlet at 3.24 ppm, 2H multiplet at 3.34-3.95 ppm; mass spectrum, m/e (rel. intensity) 172(M⁺, 1), 154(44), 141(24), 117(26), 115(22), 111(29), 109(22), 108(29), 101(100), 97(64), 96(41), 91(64), 81(38), 80(38), 79(30), 67(20), 55(40).

Anal. Calcd for C₉H₁₆O₃: C, 62.76; H, 9.37. Found: C, 62.55; H, 9.29.

7,7-Dimethoxynorbornan-2-one (IX)

A 1-l. three-necked round bottom flask was equipped with a magnetic stirrer, a thermometer immersed in the reaction mixture and a nitrogen inlet tube. In the flask was placed 100 ml of anhydrous pyridine, and the flask was cooled in an ice-water bath to 15-20°C. Chromium trioxide (10.0 g.) was added in small amounts to the stirred solvent at a rate so as to keep the temperature below 30°C. After about one-third of the CrO₃ was added, the yellow complex began to precipitate. At the end of the addition (about 1 hour), a slurry of the yellow-orange complex in

pyridine remained. The temperature of the stirred solution was readjusted to 15°C., and the stirring at this temperature was continued until the precipitate reverted to a deep red macrocrystalline form. Petroleum ether (200 ml.) was then added to the reaction mixture, the precipitate was allowed to settle, and the solvent mixture was decanted. The residue was washed three times with 200 ml of petroleum ether with the solvent being removed each time by decantation. The precipitate was dried by passing nitrogen over it. Dry methylene chloride was added to make a 5% solution. A solution of 16.5 g. (0.096 mole) of (VIII) in 20 ml. of dry methylene chloride was added with stirring to the chromium trioxide-pyridine complex at room temperature. The oxidation was complete in about 15 minutes with a black precipitate forming. The solvent was removed by a rotary evaporator leaving the crude product which was distilled to yield 13.3 g. (0.078 mole, 82%) of (IX), b.p. 71-72°C (1-2mm); m.p. 32-33°C; IR(CDCl₃, cavity cell) 2950(s), 1760(s), 1200(m), 1150(m), 1110(m), 1080(m); NMR (CDCl₃, TMS) 6H multiplet at 1.27-2.57 ppm, 3H singlet at 3.23 ppm, 3H singlet at 3.26 ppm, 2H multiplet at 3.07-3.30 ppm; mass spectrum, m/e (rel. intensity) 170(M⁺, 14), 155(2), 139(10), 123(4), 115(8), 101(100), 97(34), 67(8), 59(8), 55(32), 41(18), 39(12).

Anal. Calcd for C₉H₁₄O₃: C, 63.51; H, 8.29. Found: C, 63.62; H, 8.40.

2-Methylene-7,7-dimethoxynorbornane (X)

A solution of sodium methylsulfinyl carbanion was prepared according to the procedure of Corey.²⁶ Into a three-necked, 500 ml. round bottom flask, was placed 3.84 g. (0.08 mole) sodium hydride (50% mineral oil dispersion). The sodium hydride was washed three times with

petroleum ether by swirling allowing the hydride to settle, and decanting the liquid portion in order to remove the mineral oil. The flask was immediately fitted with a magnetic stirrer, a reflux condenser, and a pressure-equalizing dropping funnel. A three way stopcock, connected to the top of the reflux condenser, was connected to a water aspirator and a source of dry nitrogen. The system was evacuated until the last traces of petroleum ether were removed from the sodium hydride and was then flushed with nitrogen by evacuating and filling the nitrogen several times. The aspirator hose was removed and this arm of the stopcock was connected to a bubbler to which the system is opened. Dimethyl sulfoxide which was distilled from calcium hydride (b.p. $64^{\circ}/4$ mm) was introduced through the dropping funnel and the mixture was heated with stirring to $70-75^{\circ}\text{C}$ until the evolution of hydrogen ceases which usually was about 45 minutes. The solution was cooled in a cold water bath and stirred during the addition of 17.8 g. (0.077 mole) of (methyl)-triphenylphosphonium bromide in 50 ml. of warm dimethyl sulfoxide whereupon the deep red color of the ylide was produced. After stirring for 15 minutes the ketone (IX) in 10 ml. of dimethyl sulfoxide was added with stirring in a cold water bath. The reaction mixture was heated to 60° for four hours. The reaction mixture was then cooled and poured into 500 ml. of cold water. The mixture was extracted three times with pentane, washed once with water, dried over anhydrous sodium sulfate, filtered and the solvent removed by rotary evaporation. The crude product was distilled to provide 10.0 g (0.06 mole, 77%) of (X), b.p. $76-80^{\circ}\text{C}$ (15 mm); n_{D}^{26} 1.4575; IR(neat, film) 3060(w), 2940(s), 2820(m), 1670(m), 1325(s), 1280(m), 1200(m), 1170(m), 1130(m), 1100(m), 1080(s), 880(s); NMR(CDCl_3 , TMS) 8H

multiplet at 0.83-2.67 ppm, 3H singlet at 3.16 ppm, 3H singlet at 3.18 ppm, 2H multiplet at 4.51-4.83 ppm; mass spectrum, m/e (rel. intensity) 168(M^+ , 60), 153(15), 137(60), 123(13), 121(25), 105(40), 95(12), 93(100), 91(20), 79(30), 77(10), 75(10), 59(32).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.25; H, 9.69.

2-Methyl-7,7-dimethoxynorbornane (XI)

In a hydrogenation flask, (X) was added to 10 ml. of 95% ethanol and 0.3 g. of 5% palladium on carbon. This mixture was stirred under hydrogen at room temperature until the amount of hydrogen (1344 ml.) had been taken up. The catalyst was removed by filtration, and the crude product was purified and the exo- and endo-isomers were separated by preparative gas chromatography using a 6-foot, 1/2 inch inner diameter, 20% carbowax 20 M on chromosorb W-NAW at 125°C with a flow rate of 6.5 cm^3 /minutes. The crude products' ir and 1H nmr matched a similar mixture of the glc collected isomers' ir and 1H nmr spectra, thus insuring that no decomposition on the column was taking place. The exo-ketal (XIa) was in a ratio of 7:1 with the endo-ketal (XIb). The first compound eluted was identified as endo-2-methyl-7,7-dimethoxynorbornane (XIb); n_D^{25} 1.4501; IR(neat, film) 2940(s), 2860(m), 2820(s), 1450(s), 1380(m), 1325(s), 1270(m), 1200(s), 1140(s), 1100(s), 1080(s), 1060(s), 1030(m), 1000(s); NMR ($CDCl_3$, TMS) 3H doublet at 0.95 ppm, $J = 6$ Hz, 9H multiplet at 1.17-2.34 ppm, 6H singlet at 3.17 ppm; mass spectrum, m/e (rel. intensity) 170(M^+ , 100), 155(97), 139(59), 129(42), 115(89), 101(97), 97(66), 55(63).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.42; H, 10.62.

The second compound eluted was identified as exo-2-methyl-7,7-dimethoxynorbornane (XIa); n_D^{25} 1.4320; IR(neat, film) 2950(s), 2860(m), 2820(s), 1450(s), 1330(s), 1270(m), 1200(s), 1140(s), 1100(s), 1075(s), 1055(s), 1030(m), 1000(s); NMR ($CDCl_3$, TMS) 3H doublet at 1.05 ppm, $J = 6$ Hz, 9H multiplet at 0.80-2.05 ppm, 3H singlet at 3.16 ppm, 3H singlet at 3.17 ppm; mass spectrum, m/e (rel. intensity) 170(M^+ , 100), 155(75), 139(60), 138(20), 129(50), 115(80), 101(90), 97(70), 55(70).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.51; H, 10.60.

Exo-2-methyl-7-norbornanone (II)

Into a 50 ml Erlenmeyer flask equipped with a magnetic stirrer, the exo-ketal (XIa) (2.50 g, 14.7 mmole) was added to 25 ml of 5% H_2SO_4 and stirred for 12 hours at room temperature. Afterwards, this mixture and 25 ml of diethyl ether were placed into a separatory funnel. The ether layer was separated and the aqueous layer was washed twice with diethyl ether. The combined ethereal fractions were then washed with water, saturated sodium bicarbonate, water, saturated sodium chloride and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration. The ether was reduced to a volume of 20 ml by a rotary evaporator. The crude ketone was purified by preparative gas chromatography on a 10-foot, 1/4 inch inner diameter column, 20% Carbowax 20M on Chromosorp W-NAW at 125°C with a flow of 30 ml of He/min. No starting ketal was observed in the glc trace. With these conditions, the ketal would have had a retention time of 10.5 minutes. The product had a retention time of 15.0 minutes. The compound was identified as exo-2-methyl-7-norbornanone (II); n_D^{25} 1.4490; IR(neat, film) 2940(s), 2850(w), 1840(w), 1765(s), 1730(w),

1450(m), 1140(s); NMR (CDCl_3 , TMS) 3H doublet at 0.96 ppm, $J = 6$ Hz, 9H multiplet at 1.33–2.17 ppm [lit.²⁷ NMR (CDCl_3 , TMS) 3H doublet at 0.96 ppm]; mass spectrum, m/e (rel. intensity) 124(M^+ , 80), 109(25), 95(60), 93(50), 81(90), 68(40), 67(50), 55(100).

Anal. Calcd for $\text{C}_8\text{H}_{12}\text{O}$: C, 77.37; H, 9.74. Found: C, 77.30; H, 9.72.

Endo-2-methyl-7-norbornanone (III)

The same procedure used to convert the exo-ketal to the exo-ketone (II) was used to convert the endo-ketal (XIb) to the endo-ketone (III). Again, under the same conditions described above for the purification and isolation of the exo-ketone, no starting ketal (XIb) was observed in the glc trace. Under these conditions the ketal would appear after 11.5 minutes and the endo-ketone appeared after 16.5 minutes. This ketone was identified as endo-2-methyl-7-norbornanone (III); n_D^{25} 1.4661; IR(neat, film) 2940(s), 2850(m), 1860(w), 1740(vs), 1470(m), 1450(m), 1145(s); NMR (CDCl_3 , TMS) 3H doublet at 1.10 ppm, $J = 6$ Hz, 9H multiplet at 1.62–2.42 ppm [lit.²⁷ NMR (CDCl_3 , TMS) 3H doublet at 1.10 ppm]; mass spectrum, m/e (rel. intensity) 124(M^+ , 83), 109(12), 95(79), 93(34), 81(98), 68(41), 67(52), 55(100).

Anal. Calcd for $\text{C}_8\text{H}_{12}\text{O}$: C, 77.37; H, 9.74. Found: C, 77.32; H, 9.70.

5-Methyl-7,7-dimethoxy-1,2,3,4-tetrachloronorborn-2-ene (XII) (1:9 Mixture of exo- to endo-isomers)

A mixture of propylene and nitrogen was bubbled in to 264 g. (1 mole) of (IV) under the same conditions used to prepare (V). Compound (IV) was preheated to 190°C in a 500 ml. one-necked round bottom flask.

fitted with a fritted glass gas inlet tube and a magnetic stirrer. Once the starting material reached a temperature of 190°C , the gas was introduced and these conditions were maintained for 6 hours with stirring. After the desired time, the reaction mixture was cooled and distilled to provide 230.0 g. (0.75 mole, 75%), of a pale-yellow syrup identified as (XII); b.p. $88-91^{\circ}\text{C}$ (0.7 mm) n_{D}^{25} 1.5204; IR(neat, film) 2960(m), 2940(s), 2835(s), 1620(w), 1610(s), 1450(s), 1380(m), 1275(s), 1200(s), 1130(s), 1095(s), 1030(m), 1000(m), 965(m), 910(m), 785(s), 760(s); mass spectrum, m/e (rel. intensity) 268(M^{+} -38,6), 267(2), 266(14), 265(4), 264(36), 263(6), 262(38), 261(2), 257(15), 255(30), 253(15), 249(33), 247(24), 239(9), 237(15), 235(36), 233(58), 231(61), 229(100), 227(79), 225(21), 223(33), 221(48), 220(52), 219(39), 218(88), 216(82), 214(27), 212(33), 190(64), 120(61), 118(79), 59(79); NMR (CDCl_3 , TMS) 3H doublet at 0.92 ppm $J = 6$ Hz, 3H multiplet at 1.21-2.75 ppm, 3H singlet at 3.51 ppm, 3H singlet at 3.56 ppm.

Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{Cl}_4\text{O}_2$: C, 39.24; H, 3.95. Found: C, 39.11; H, 3.89.

A 10% SE-30 on Chromosorb W column at 180°C with a flow rate of 55 ml of He/min providing a glc trace which showed a 1 to 9 ratio of the exo- and endo-isomers. The isomers were not separated at this stage of the synthesis.

5-Methyl-7,7-Dimethoxynorborn-2-ene (XIII) (A 1:9 Ratio of Exo- to Endo-Isomers)

To a vigorously stirred solution of 90 g. (1.22 moles) of t-butyl alcohol, 525 ml. of freshly distilled tetrahydrofuran, and 59 g. (2.57 g-atoms) of finely chopped sodium metal under a nitrogen atmosphere in a

1-1 three-necked round bottom flask equipped with a magnetic stirrer, a pressure-equalizing dropping funnel fitted with a rubber serum cap and a condenser fitted with a three-way stopcock connected to a mineral oil filled bubbler was added 30.6 g. (0.1 mole) of (XII). The mixture was heated gently to maintain a steady reflux for 10 hours. After cooling, the excess sodium was destroyed by slow addition of methanol (about 500 ml.) to the reaction mixture. The reaction mixture was poured over 2 l. of ice and the reaction flask was washed with approximately 600 ml. of water. The solution was extracted with three 250 ml. portions of water and once with saturated sodium chloride solution. The ethereal solution was dried over anhydrous sodium sulfate and filtered. The glc confirmed the crude product contained both the exo- and endo-isomers in a 10 to 90 ratio. The crude product was distilled to give 9.8 g. of the mixture of isomers (59% yield), b.p. 73-78°C (13 mm); n_D^{25} 1.4601; IR(neat, film) 3060(m), 2950(s), 2840(m), 2820(m), 1600(m), 1450(s), 1300(s), 730(s); NMR (CDCl₃, TMS) 3H doublet at 0.76 ppm $J = 6.5$ Hz, 2H multiplet at 0.30-1.38 ppm, 1H multiplet at 1.78-2.32 ppm, 2H multiplet at 2.47-2.73 ppm, 3H singlet at 3.02 ppm, 3H singlet at 3.12 ppm, 2H multiplet at 5.83-6.20 ppm; mass spectrum, m/e (rel. intensity) 168(M⁺, 60), 153(46), 137(46), 123(30), 93(100).

Anal. Calcd for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.50.

Hydrogenation of (XIII)

In a hydrogenation flask, 9.8 g. of (XIII), was added to 10 ml. of 95% ethanol and 0.10 g. of 5% palladium on carbon. This mixture was stirred under hydrogen at room temperature. After the hydrogen absorption had ceased, the catalyst was removed by filtration. The crude product was purified and the exo- and endo-isomers were separated by preparative glc using a 15 ft. 20% Carbowax 20 M on Chromosorp W-NAW column at 130°C with a flow of 30 ml/min yielding a 9:1 ratio of endo- and exo-ketals. The mmr, ir and mass spectrum as well as glc retention times of these compounds were identical to the exo- and endo-ketals, (XIa) and (XIb), prepared above.

7-Norbornanol (XIV)

Into a 250-ml. three-necked round bottom flask equipped with a magnetic stirring bar and fitted with a three-way stopcock with one arm connected to a mineral oil filled bubbler and a pressure-equalizing dropping funnel fitted with a rubber serum cap, a solution of 1.03 g. (9.30 mmole) of ketone (I) in 20 ml. of distilled Et₂O was placed. After cooling the flask and contents to 0° C, a solution of .741 g. (19 mmole) of LiAlH₄ in 40 ml of Et₂O was added dropwise with stirring. After addition was complete the solution was stirred for 2 hours whereupon 3 ml. of water was added dropwise to the stirring solution of 0°C. The resulting slurry was stirred for 0.5 hour, filtered, and the precipitate washed with Et₂O. The filtrate was dried over anhydrous magnesium sulfate and the drying agent was removed by filtration. The ether was removed by flash evaporation to provide 0.897 g. (86%) of

(XIV), m.p. 151-153°C. The white crystals were recrystallized from hexane to give pure (XIV), m.p. 152-153°C (lit.²⁸ m.p. 152-153°C).

Birch Reduction of (II)

To a 100 ml. three-necked round bottom flask equipped with a magnetic stirrer, dry ice-acetone condenser and a stopper was added 50 ml. of condensed anhydrous ammonia, 0.122 g. (0.001 mole) of (II) and 2.5 ml. of absolute ethanol. To this stirred reaction mixture, 0.7 g. of finely chopped sodium metal was added. A deep blue color was produced. Stirring was continued for 15 minutes and the ammonia allowed to evaporate after the addition of 2.5 ml. of water. The mixture was extracted twice with hexane. The combined hexane extracts were washed with water and saturated sodium chloride solution and then dried with anhydrous sodium sulfate. The hexane was removed by rotary evaporation. The residue showed two peaks on the gas chromatograph using a 15 ft., 20% carbowax 20 M on chromosorp W-NAW column in a 20:80 ratio.

The first compound, minor product, eluted was identified as exo-2-methyl-syn-7-norbornanol, (XVa); n_D^{26} 1.4507; IR(neat, film) 3600-3000(broad-s), 2940(s), 2860(s), 1450(s), 1380(s), 1360(s), 1340(m), 1310(s), 1170(s), 1160(s), 1110(s), 1090(s), 1050(m), 1120(m), 850(m); mass spectrum, m/e (rel. intensity) 126(M⁺, 7), 111(35), 108(63), 97(43), 95(90), 93(55), 91(15), 84(20), 83(20), 82(30), 79(30), 71(25), 70(100), 69(25), 67(60), 57(62), 55(55), 53(15), 43(20), 41(40), 40(30), 39(30); ¹H NMR (CDCl₃, TMS) 3H doublet at 0.91 ppm J= 6 Hz, 10H multiplet at 1.05-2.15 ppm, 1H singlet at 3.97 ppm; ¹³C NMR(CDCl₃, multiplicity in off-resonance decoupling) C(7), 80.38 ppm (d); C(1), 46.29 ppm (d); C(2), 41.37 ppm (d); C(4), 36.95 ppm (d); C(3), 36.34 ppm

(t); C(6), 27.73 ppm (t); C(5), 25.60 ppm (t); C(8), 22.33 ppm (q).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.01; H, 11.23.

The second compound, major product, was identified as exo-2-methyl-anti-7-norbornanol, (XVb); n_D^{26} 1.4625; IR(neat, film) 3600-3000 (broad-s), 2940(s), 2860(s), 1450(s), 1380(s), 1360(s), 1340(m), 1320(s), 1180(s), 1150(s), 1110(s), 1080(s), 1050(m), 1020(m), 840(m); mass spectrum, m/e (rel. intensity) 126(M^+ , 10), 111(18), 108(33), 97(16), 95(81), 93(64), 91(14), 84(24), 83(25), 82(34), 79(26), 71(34), 70(100), 69(28), 67(55), 57(50), 55(53), 53(19), 43(26), 41(40), 39(33); 1H NMR ($CDCl_3$, TMS) 3H doublet at 1.12 ppm $J = 6$ Hz, 10H multiplet at 1.05-2.15 ppm, 1H singlet at 4.10 ppm; ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) C(7), 77.90 ppm (d); C(1), 46.66 ppm (d); C(2), 41.07 ppm (d); C(4), 36.77 ppm (d); C(3), 34.89 ppm (t); C(6), 27.06 ppm (t); C(5), 29.60 ppm (t); C(8), 22.02 ppm (q).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.05; H, 11.25.

Endo-2-Methyl-7-Norbornanol (XVI)

The same procedure used to prepare 7-norbornanol (XIV) was followed to prepare the syn- and anti-endo-2-methyl-7-norbornanols (XVa) and (XVb), respectively. A solution of ketone (III) in Et_2O was added dropwise to the calculated amount of LAH in Et_2O . After the normal work up, the crude alcohols were obtained in an Et_2O solution. This solution was subjected to the aforementioned glc conditions and only one peak was observed which was expected since the steric environment for both isomers is essentially the same. These isomers were collected together

via preparative glc. The collected mixture had the following properties: m.p. 51-59°C; IR (CDCl_3 , Cavity Cell) 3600(sharp-s), 3550-3050(broad-s), 1480(s), 1450(s), 1380(s), 1350(s), 1300(s), 1260(m), 1230(w), 1175(w), 1075(s), 1050(w); mass spectrum, m/e (rel. intensity) 126(M^+ , 7), 111(17), 109(43), 97(29), 95(100), 93(95), 85(14), 84(24), 83(29), 82(29), 81(14), 80(24), 79(29), 77(19), 71(43), 70(100), 69(33), 68(24), 67(38), 57(38), 43(38), 41(57), 40(71), 39(38); ^1H NMR (CDCl_3 , TMS) 3H doublet at 1.02 ppm $J = 7$ Hz, 9H multiplet at 0.53-2.50 ppm, 1H singlet at 2.48 ppm, 1H broad singlet at 4.08 ppm. The ^{13}C NMR was conducted in order to confirm the existence of both isomers. Based on literature values,²⁹ the following assignments were made for endo-2-methyl-syn-7-norbornanol (XVIa) and endo-2-methyl-anti-7-norbornanol (XVIb): (XVIa) ^{13}C NMR (CDCl_3 , multiplicity in off-resonance decoupling) C(7), 81.05 ppm (d); C(1), 45.38 ppm (d); C(2), 41.32 ppm (d); C(4), 35.67 ppm (d); C(3), 29.91 ppm (t); C(6), 27.24 ppm (t); C(5), 19.54 ppm (t); C(8), 16.44 ppm (q). (XVIb) ^{13}C NMR (CDCl_3 , multiplicity in off-resonance decoupling) C(7), 80.02 ppm (d); C(1), 45.75 ppm (d); C(2), 41.62 ppm (d); C(4), 35.98 ppm (d); C(3), 30.34 ppm (t); C(6), 27.29 ppm (t); C(5), 19.17 ppm (t); C(8), 17.29 ppm (q). The ratio of (XVIa) to (XVIb) was determined to be approximately 50:50 by comparing the intensities of the ^{13}C NMR lines associated with the C(7)s and C(8)s of each compound (see eqs. 3 and 4).

Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}$: C, 76.14; H, 11.18. Found: C, 76.20; H, 11.23.

Reductions of Ketones (I), (II) and (III)

A 5 ml Erlenmeyer flask equipped with a magnetic stirring bar, was flash flamed, cooled and fitted with a rubber serum cap under nitrogen.

To the flask was added the calculated amount of each ketone in THF or Et_2O along with the internal standard which was hexadecane. The calculated amount of reducing agent was then added to the stirred mixture at the desired temperature. After the desired time, usually two hours, the reaction was quenched with water or saturated ammonium chloride solution. The organic layer was separated and dried over anhydrous sodium sulfate and then subjected to glc conditions for identification of products. A 15 ft. 20% Carbowax 20 M on Chromosorb W-NAW column at 135°C with a flow rate of 30 ml of He/min was used to effect separation of all products. Inverse addition of reactants provided the same results. The following was the order of elution of the products on this column at these conditions: ketone (I), 12.0 minutes; ketone (II), 20.0 minutes; ketone (III), 25.2 minutes; alcohol (XIV), 26.3 minutes; alcohol (XVa), 33.0 minutes; alcohols (XVIa) and (XVIb), 38.3 minutes; alcohol (XVb), 41.4 minutes; and hexadecane, 48.0 minutes. In all cases, only alcohol (XVa) was produced when ketone (II) was reduced. As noted before, the isomers of alcohol (XVI) could not be separated by any technique but could be identified by ^{13}C NMR.

Meerwein-Ponndorf-Verley Reduction of Ketone (II)

Into a 50 ml one-necked round bottom flask fitted with a partial reflux head and a magnetic stirrer was placed 2 ml of 0.032 M solution of ketone (II) in diethyl ether along with 1.0 g aluminum isopropoxide and 5 ml of isopropyl alcohol. This mixture was heated to 50°C and stirred for 2 days. After cooling to room temperature, the mixture was poured into 100 ml of saturated aqueous ammonium chloride and the solution extracted with two 10 ml portions of ether. The ethereal

extracts were combined and washed with water and saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The ether was partially removed by use of a water aspirator. This solution was then analyzed as before by glc. The only product was the anti-alcohol.

Meerwein-Ponndorf Equilibration of (XVa) and (XVb)

Into a 50 ml one-necked round bottom flask equipped with a magnetic stirrer was added 100 mg of syn-2-exo-methyl-7-norbornanol (XVa), 1 g of aluminum isopropoxide, 5 ml of isopropanol and 5 ml of acetone. Mild heat was applied with stirring for 3 days. The glc analysis of the hydrolyzed mixture was shown to contain the anti-alcohol almost exclusively except for a trace of the syn-alcohol.

7-Methyl-7-Norbornanol (XVII)

Into a 250 ml three-necked round bottom flask equipped the same as for the preparation of 7-norbornanol (XIV), was placed a solution of 1.05 g (9.31 mmole) of ketone (I) in 20 ml of freshly distilled Et₂O. To this mixture, a solution of 40 ml of 0.51 M MeMgBr (20.4 mmole) in Et₂O is added dropwise with stirring. After the addition was complete, the solution was stirred for 2 hours and then quenched and worked up in the usual manner. The ether was removed by rotary evaporation to provide 1.02 g (87%) of white crystals which were sublimed at 70-80°C (15mm) to give pure (XVII), m.p. 95-96°C; IR(CCl₄, cavity cell) 3625 cm⁻¹ [lit.³⁰ m.p. 97-98°C, IR (CCl₄, cavity cell) 3618 cm⁻¹].

Syn-2-Exo-Methyl-7-Methyl-7-Norbornanol (XVIIIa)

This alcohol was prepared by the same procedure used to prepare alcohol (XVII). Ketone (II) was allowed to react with methylmagnesium bromide which was prepared by the reaction of magnesium metal with

methylbromide in Et_2O in a Grignard to ketone ratio of 2:1. After the addition, the resulting solution was stirred for two hours and then quenched and worked up in the usual manner. The product was then analyzed on a 10 ft. 20% FFAP on Diatoport S column at 150°C and flow rate of 30 ml of He/min. Only one compound was observed at these conditions. The product was identified as syn-2-exo-methyl-7-methyl-7-norbornanol (XVIIIa); m.p. $51-52^\circ\text{C}$; IR (CDCl_3 , Cavity Cell) 3600(sharp-m), 2950(s), 2870(m), 1480(m), 1450(m), 1380(s), 1315(w), 1300(w), 1265(w), 1225(m), 1200(w), 1185(w), 1170(m), 1110(s), 960(m), 950(s); mass spectrum, m/e (rel. intensity) 140(M^+ , 7), 125(52), 122(15), 111(9), 107(7), 97(33), 93(14), 85(24), 84(17), 83(10), 82(24), 81(19), 71(57), 69(14), 67(21), 55(53), 43(100), 41(24), 39(17); ^1H NMR (CDCl_3 , TMS) 3H doublet at 1.21 ppm $J = 6$ Hz, 3H singlet at 1.35 ppm, 10H multiplet at 0.95-1.83 ppm; ^{13}C NMR (CDCl_3 , multiplicity in off-resonance decoupling) C(7), 84.15 ppm (d); C(1), 49.45 ppm (d); C(2), 44.96 ppm (d); C(4), 38.59 ppm (d); C(3), 38.58 ppm (t); C(6), 29.18 ppm (t); C(5), 26.63 ppm (t); C(9), 22.51 ppm (q); C(8), 22.14 ppm (q).

Anal. Calcd for $\text{C}_9\text{H}_{16}\text{O}$: C, 77.08; H, 11.50. Found: C, 76.91; H, 11.59.

Anti-2-Exo-Methyl-7-Methyl-7-Norbornanol (XVIIIb)

Into a 50 ml one-necked round bottom flask fitted with a magnetic stirring bar, 25 ml of 20% H_2SO_4 and 2 mmole (0.28g) of (XVIIIa). This reaction mixture was stirred for 2 days at 80°C . Afterwards, the solution was cooled and 20 ml of Et_2O was added. The ethereal layer was separated, washed with water, saturated sodium chloride and dried over anhydrous sodium sulfate. Subjecting the product to the same glc conditions used

for the syn-alcohol, two compounds were observed. The first compound eluted matched the retention time for the syn-alcohol and was in a 2:1 ratio with the other compound which was identified as the anti-alcohol (XVIIIb); m.p. 49-50°C; IR (CDCl₃, Cavity Cell) 3590(w), 3330(broad-s), 2950(s), 2860(s), 1485(w), 1450(m), 1380(s), 1350(m), 1300(m), 1245(m), 1220(m), 1190(m), 1130(s), 1100(s), 950(s); mass spectrum, m/e (rel. intensity) 140(M⁺, 10), 125(35), 122(1), 111(15), 107(10), 97(50), 93(20), 85(15), 84(10), 82(15), 81(23), 71(60), 69(15), 67(20), 55(70), 43(100), 41(20), 39(25); ¹H NMR (CDCl₃, TMS) 3H doublet at 1.07 ppm J = 7 Hz, 3H singlet at 1.46 ppm, 10H multiplet at 0.96-2.17 ppm; ¹³C NMR (CDCl₃, multiplicity in off-resonance decoupling) C(7), 83.06 ppm (d); C(1), 49.69 ppm (d); C(2), 44.90 ppm (d); C(4), 37.68 ppm (d); C(3), 36.16 ppm (t); C(6), 30.52 ppm (t); C(5), 27.30 ppm (t); C(9), 22.57 ppm (q); C(8), 21.42 ppm (q).

Anal. Calcd for C₉H₁₆O: C, 77.08; H, 11.50. Found: C, 77.20; H, 11.35.

The first compound eluted which matched the retention time of the syn-alcohol was also isolated and it was indeed confirmed to be the syn-alcohol by its ir, nmr and mass spectra.

Endo-2-Methyl-7-Methyl-7-Norbornanol (XIX)

The same procedure used to prepare 7-methyl-7-norbornanol (XVII) was followed to prepare the syn- and anti-endo-alcohols (XIXa) and (XIXb). A solution of ketone (III) in freshly distilled diethyl ether was added dropwise to a 100% excess of MeMgBr in diethyl ether. After the normal reaction time, the usual work up procedure was followed. The crude alcohols were analyzed on a 10 ft. 20% FFAP on Diatoport S column

at 150°C with a flow rate of 30 ml of He/minute. Only one peak was observed under these conditions, but again this is not surprising since the steric environment is essentially the same for both isomers. By preparative glc, these isomeric alcohols were collected together and the following spectra values were obtained: m.p. 28-29°C; IR (CDCl₃, Cavity Cell) 3600-3050(s), 2950(s), 2860(s), 1485(s), 1380(s), 1350(m), 1315(s), 1300(m), 1265(m), 1245(m), 1220(s), 1200(s), 1190(m), 1150(m), 1130(s), 1100(s), 1080(w), 1060(w), 945(s); mass spectrum, m/e (rel. intensity) 140(M⁺, 17), 125(40), 122(19), 111(13), 107(31), 97(67), 96(24), 93(62), 85(52), 84(52), 83(24), 82(44), 81(34), 80(16), 79(23), 71(94), 70(28), 69(22), 67(43), 55(51), 43(100), 41(28), 39(22); ¹H NMR (CDCl₃, TMS) 3H doublet at 0.96 ppm J = 6 Hz, 3H singlet at 1.40 ppm, 10H multiplet at 0.50-2.50 ppm.

The ¹³C NMR of these alcohols showed 18 lines indicating the existence of two alcohols. Based on literature values²⁹ the following assignments were made: syn-2-endo-methyl-7-methyl-7-norbornanol (XIXa) ¹³C NMR (CDCl₃, multiplicity in off-resonance decoupling) C(7), 85.00 ppm (d); C(1), 48.66 ppm (d); C(2), 44.84 ppm (d); C(4), 37.86 ppm (d); C(3), 31.25 ppm (t); C(6), 28.21 ppm (t); C(5), 21.23 ppm (t); C(9), 19.90 ppm (q); C(8), 17.05 ppm (q). Anti-2-endo-methyl-7-methyl-7-norbornanol (XIXb) ¹³C NMR (CDCl₃, multiplicity in off-resonance decoupling) C(7), 84.27 ppm (d); C(1), 49.02 ppm (d); C(2), 44.92 ppm (d); C(4), 37.13 ppm (d); C(3), 30.58 ppm (t); C(6), 29.06 ppm (t); C(5), 20.63 ppm (t); C(9), 20.45 ppm (q); C(8), 17.72 ppm (q).

Anal. Calcd for C₉H₁₆O: C, 77.08; H, 11.50. Found: C, 76.91; H, 11.44.

The ratio of (XIXa) to (XIXb) was determined to be approximately 50:50 by comparing the intensities of the ^{13}C NMR lines associated with the C(9)s and C(8)s of each compound (see eqs. 5 and 6).

Alkylations of Ketones I, II and III

A 5 ml Erlenmeyer flask equipped with a magnetic stirring bar, was flash flamed or heated in an oven, cooled and fitted with a rubber serum cap under nitrogen. To the flask was added the calculated amount of each ketone in freshly distilled THF or Et_2O along with the internal standard which was hexadecane. The calculated amount of alkylating agent was then added to the stirred mixture at the desired temperature. After the desired time, usually two hours, the reaction was quenched with water or saturated ammonium chloride solution. The organic layer was separated and dried over anhydrous sodium sulfate and then analyzed on a 10 ft. 20% FFAP on Diatoport S column at 150°C with a flow rate of 30 ml/min. Inverse addition of reactants provided the same results. The following was the order of elution of the products on this column at these conditions: ketone (I), 15.3 minutes; ketone (II), 20.2 minutes; ketone (III), 23.5 minutes; alcohol (XVIIIa), 35.0 minutes; alcohol (XVII), 39.5 minutes; alcohol XVIIIb), 43.3 minutes; alcohol (XIX), 48.2 minutes and hexadecane appeared after 29.6 minutes. In all cases, only alcohol XVIIIa was produced when ketone (II) was alkylated. As noted before, the isomers of alcohol (XIX) could not be separated by any technique but could be identified by ^{13}C NMR.

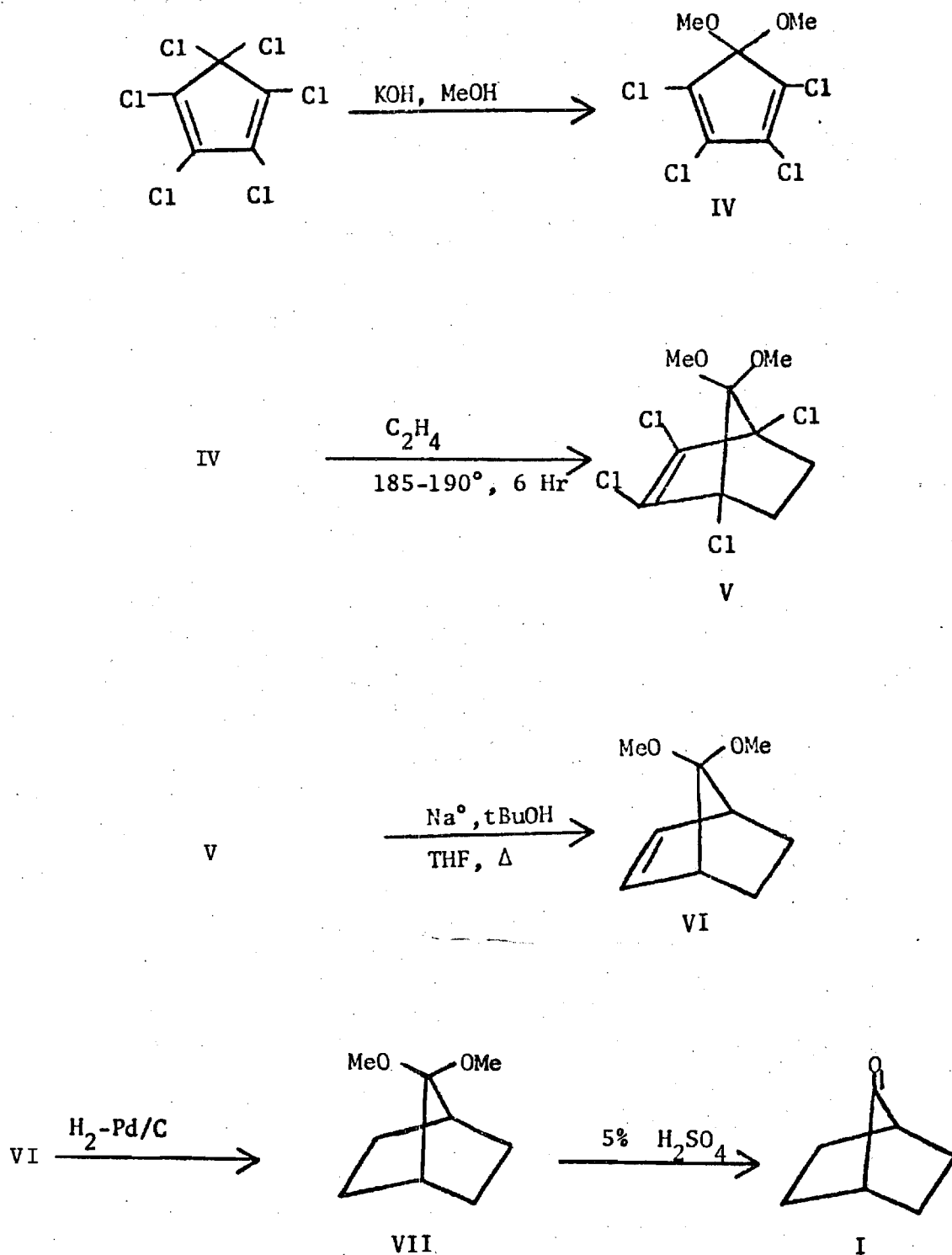
CHAPTER III

RESULTS AND DISCUSSION

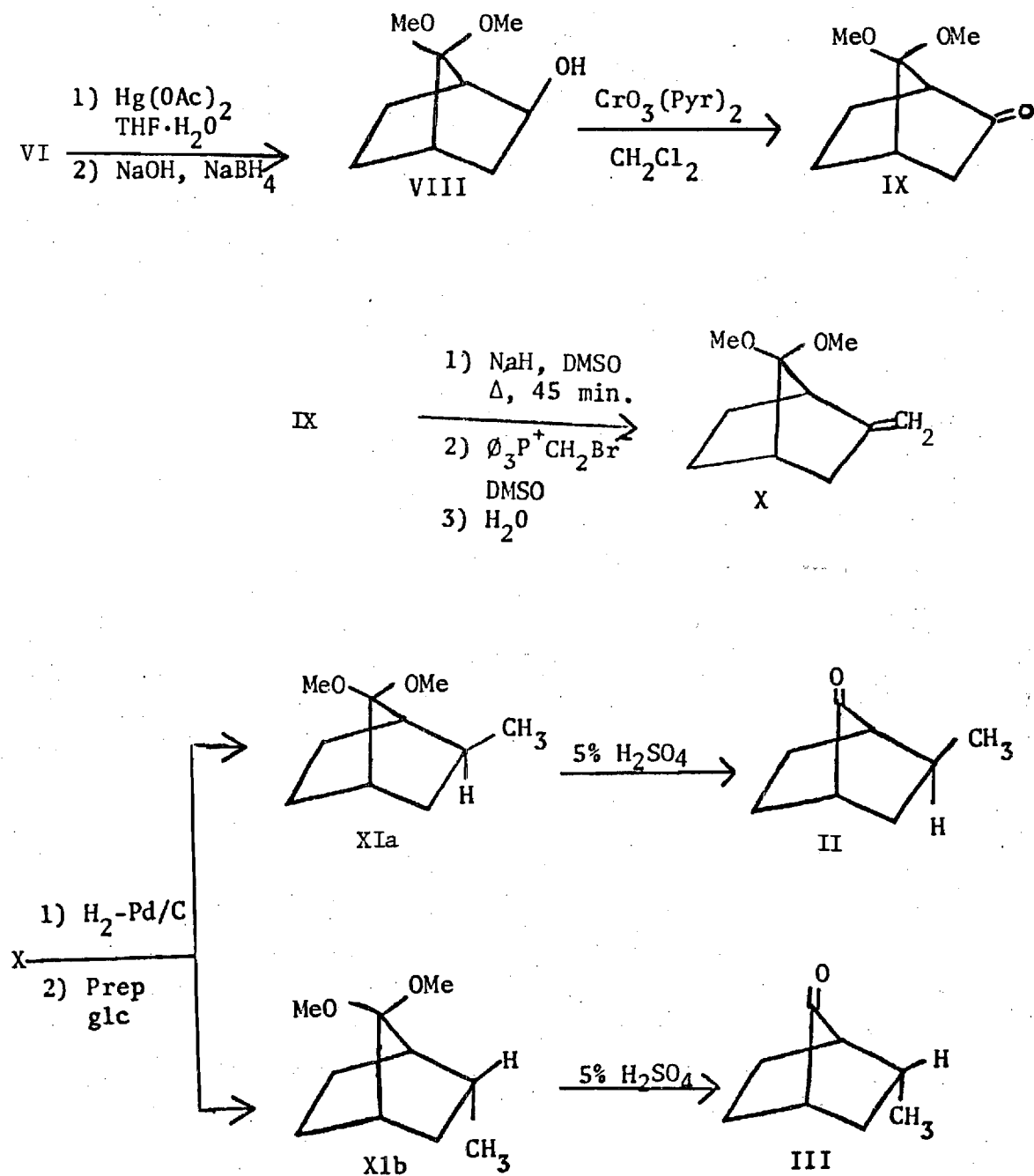
Synthesis of Model Systems for Reduction Studies

The synthesis of 7-norbornanone, (I), was accomplished by a modified procedure of Gassman and Pape²⁵ (Scheme 1). Hexachlorocyclopentadiene was allowed to react with methanolic potassium hydroxide which provided 1,1-dimethoxytetrachlorocyclopentadiene, (IV). Compound (IV) was then allowed to react under Diels-Alder conditions with ethylene to product 1,2,3,4-tetrachloro-7,7-dimethoxy-2-norbornene (V) which was then dehalogenated with sodium to produce 7,7-dimethoxy-2-norbornene (VI). 7,7-Dimethoxynorbornane (VII) was produced from the hydrogenation of (VI) with hydrogen in the presence of 5% palladium on carbon catalyst. Norbornanone (I) was produced from the deketalization of (VII) with 5% H_2SO_4 .

Exo-2-methyl-7-norbornanone (II) and endo-2-methyl-7-norbornanone (III) were prepared in a straightforward manner from 7,7-dimethoxy-2-norbornene (VI) (Scheme 2). Oxymercuration of (VI) led to an 80% yield of pure exo-2-hydroxy-7,7-dimethoxynorbornane (VIII) after distillation. Chromic acid oxidation³¹ of the alcohol in pyridine-dichloromethane afforded 7,7-dimethoxynorbornan-2-one (IX) in an 82% yield following distillation. This ketone was then converted to the corresponding methylene compound (X) using methyltriphenylphosphonium bromide and dimethylsodium in dimethylsulfoxide. Catalytic hydrogenation of (X) gave a 7:1 ratio of (II) to (III) following 5% sulfuric acid catalyzed de-



Scheme 1: Preparation of 7-Norbornanone, (I).

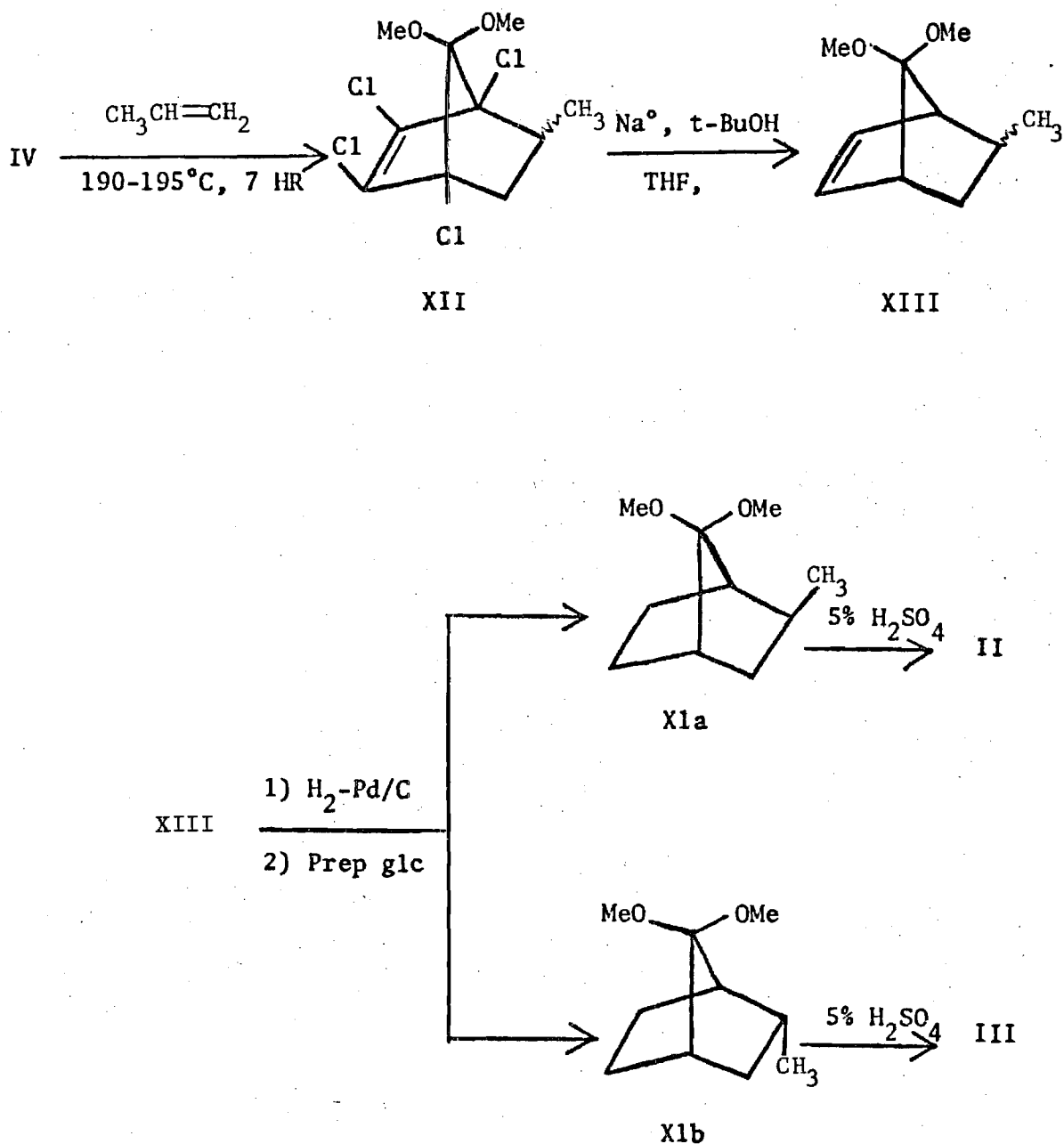


Scheme 2: Preparation of Exo-2-Methyl-7-Norbornanone (II) and Endo-2-Methyl-7-Norbornanone (III).

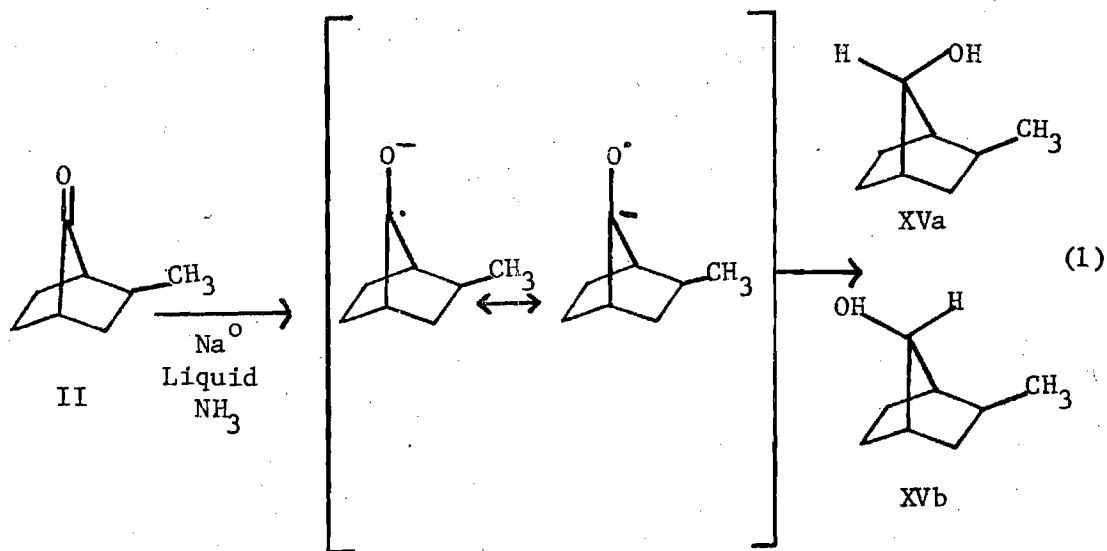
ketalization of (XIa) and (XIb). The ketones and/or ketals were separated by gas-liquid chromatography on a 15 ft. 20% carbowax 20 M on Chromosorb W-NAW column at 135°C. The NMR showed a chemical shift of 0.96 ppm for (II) and 1.10 ppm for (III). These values agreed well with those reported previously.²⁷

An alternate route for the preparation of (III) was also accomplished as shown in Scheme 3. Hexachlorocyclopentadiene was converted into 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (IV) as before. Propylene diluted with nitrogen was added to (IV) under Diels-Alder conditions giving 5-methyl-7,7-dimethoxy-1,2,3,4-tetrachloronorbornene, (XII). (XII) was then dehalogenated in the presence of sodium metal to give 5-methyl-7,7-dimethoxynorborn-2-ene, (XIII). Hydrogenation of (XIII) gave (XIa) and (XIb) in a 1:9 ratio. These ketals were then deketalized to give (II) and (III) in a 1:9 ratio.

The reduction of ketones (I), (II) and (III) was carried out using LiAlH_4 as the reducing agent. For a summary of these results, see Table I. The presence of only one alcohol as the reduced product of ketone (II) was indicated by glc and ^{13}C NMR. However, it was not possible to determine whether it was the syn or anti-alcohol. Therefore, a Birch reduction on ketone (II) was conducted. Since protonation is faster than equilibration, both the syn- and anti- alcohols should be produced (eq. 1). It was observed both by glc and ^1H NMR that both the



Scheme 3: Alternate Synthetic Route to Exo-2-Methyl-7-Norbornanone (II) and Endo-2-Methyl-7-Norbornanone (III).



syn- and anti-alcohols were produced in a 20:80 ratio. The alcohols were separated by glc and found to match the ^1H NMR spectrum reported in the literature.³² Under Meerwein-Ponndorf-Verley reduction conditions using aluminum isopropoxide and isopropanol, only the anti-alcohol from ketone (II) was produced. This indicates that under equilibrating conditions the anti-alcohol is indeed the most thermodynamically stable product. In order to substantiate this, the syn- alcohol was allowed to equilibrate under Meerwein-Ponndorf conditions employing aluminum isopropoxide, isopropanol and acetone. The anti-alcohol was formed almost exclusively except for a trace of the syn-alcohol thus further establishing the anti-alcohol is indeed the thermodynamic isomer.

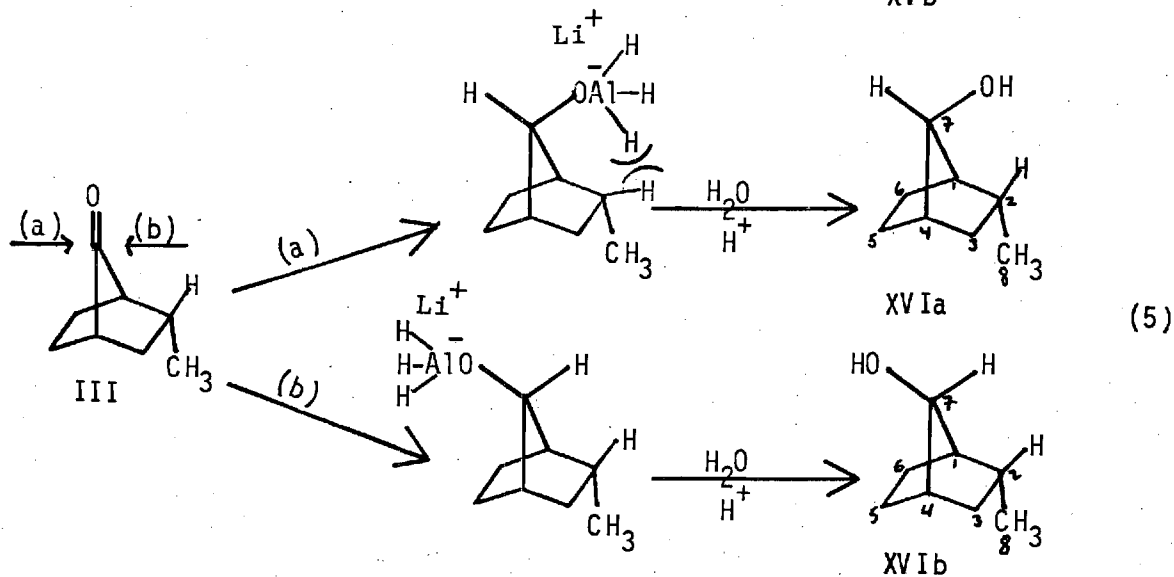
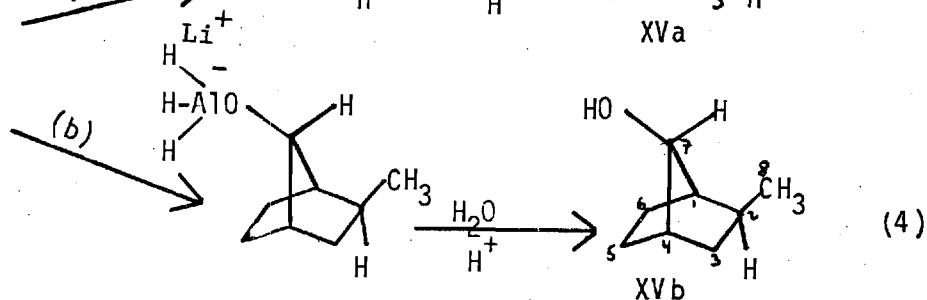
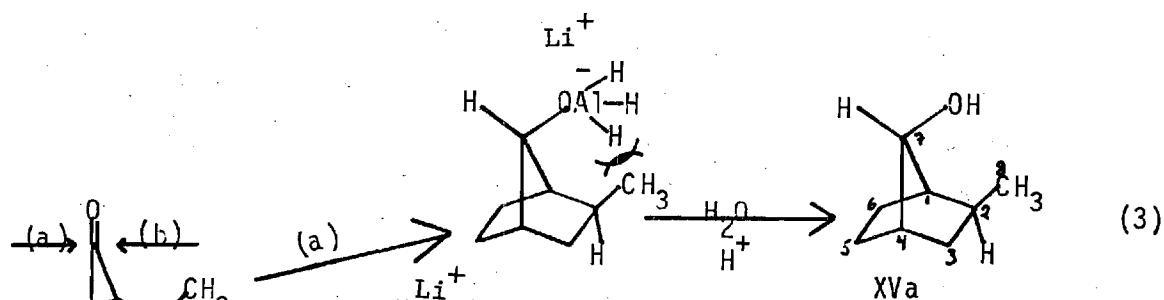
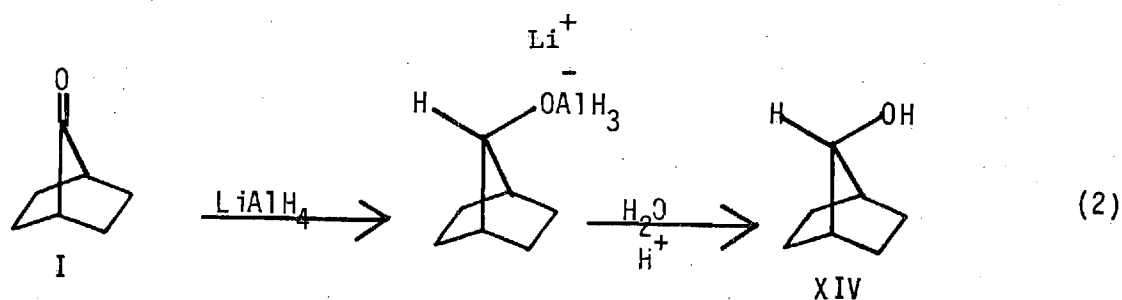
The ^{13}C NMR spectra of the Birch reduction products were also obtained. By comparing these spectra with the reduction products of LiAlH_4 with ketone (II), the latter product was confirmed as the syn-alcohol. Carbon atom assignments were made by using relative shielding

parameters and off-resonance coupling. It is known that deshielding of the carbon decreases from tetra-substituted carbons to tri-substituted to di-substituted with mono-substituted carbons appearing furthest up-field.

Stereochemistry of 7-Norbornanone Reduction

The reaction of LiAlH_4 with ketone (I) (eq. 2) or ketone (III) (eq. 5) should produce the corresponding alcohol at twice the rate of LiAlH_4 reduction of ketone (II) to produce the syn-alcohol (eq. 3) provided "product development control" is not important in this reaction. If "product development control" is important then, of course, the rate of attack on ketone (II) to produce the syn-alcohol should be decreased due to the effect of the exo-2-methyl group on the developing transition state (product development control).

Whether or not the exo-2-methyl group is sufficiently bulky to provide a valid test for "product development control" can be evaluated by comparing the syn-anti-alcohol ratio when LiAlH_4 was allowed to react with ketone (II). If the exo-2-methyl group exerts a significant steric effect in this system then significantly less anti-alcohol (eq. 4) should be produced compared to the syn-alcohol in the reaction of ketone (II) with LiAlH_4 . In order to test perturbations on the carbonyl group other than the steric effect exerted by the exo-2-methyl group, the reaction of LiAlH_4 with the endo-2-methyl-7-norbornanone, (III), was also studied. If only the steric effect of the exo-2-methyl group is significant, then the reaction of LiAlH_4 with ketone (III) to produce the syn- and anti-alcohol should proceed at the same rate as the reaction of LiAlH_4 with ketone (I) and at twice the rate compared to the formation of the syn-2-exo-methyl alcohol.



The reduction of ketones (I), (II) and (III) were carried out under identical conditions. As noted before, only one reduction product was obtained for (I) and (II), whereas (III) gave both the syn- and anti-alcohols according to glc and ^{13}C NMR. By comparing glc and ^{13}C NMR, it was substantiated that the lone reduction product of (II) was the syn-alcohol. Table 1 shows these observations as a result of anti-attack with respect to the exo-2-methyl group. This shows that the exo-2-methyl group exerts a significant steric effect with respect to attack at the 7-keto group since no anti-alcohol is observed. When ketones (I) and (II) were admixed in equal molar portions with an insufficient amount of LiAlH_4 , the alcohol products of (I) and (II) were produced in a 2:1 ratio indicating no detectable product development control. Reaction of (I) and (III) in equal molar portions with an insufficient amount of LiAlH_4 produced the corresponding alcohols in a 1:1 ratio showing that the endo-2-methyl group has no effect on the rate of reaction of the 7-keto group. Admixture of ketones (II) and (III) in equal molar ratio produce the corresponding alcohols in a 1:2 ratio and admixture of ketones (I), (II) and (III) in equal molar ratio produced the corresponding alcohols in a 2:1:2 ratio when allowed to react with an insufficient amount of LiAlH_4 . The data support the conclusion that anti-attack on ketone (II) takes place at the same rate as attack from either side of the carbonyl on ketones (I) and (III) indicating that the exo-2-methyl group although exerting a significant steric effect (no anti-exo-2-methyl alcohol formed, eq. 4) does not affect the formation of the syn-alcohol of ketone (II). When the mole ratio of ketone (II) to (III) was increased from 1:1 to 2:1 in the presence of an insufficient amount of

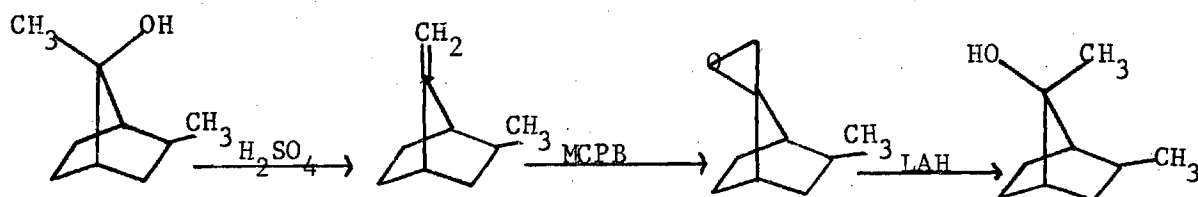
LiAlH_4 the corresponding alcohols produced were in a ratio of 1:1. This can be explained by the fact that there are now the same number of equal attack sites on both ketone (II) and (III). When the mole ratio of (II) to (III) was 4:1, the number of equal attack sites becomes 2:1. On the other hand, when the ratio of ketone (II) to (III) was 1:4, the number of equal attack sites is 1:8 which is what is reflected in the results of this experiment (Table 1). Further experiments in THF and at different stoichiometric ratios provide additional evidence for the above conclusions.

Table 2 compares the Group IIIA metal hydrides, AlH_3 , BH_3 and GaH_3 reactions with ketones (II) and (III). The results are similar to those observed for LiAlH_4 reduction indicating that the stereochemistry is independent of the steric requirement of the hydride. Similarly when LiBH_4 , LiAlH_4 and LiGaH_4 were allowed to react with ketones (I)-(III), no evidence of "product development control" was observed (Table 3). In addition when the anion (AlH_4^-) was held constant and the cation varied (Li, Na, and NR_4), no evidence of "product development control" was observed (Table 4).

Synthesis of Model Systems for Alkylation Studies

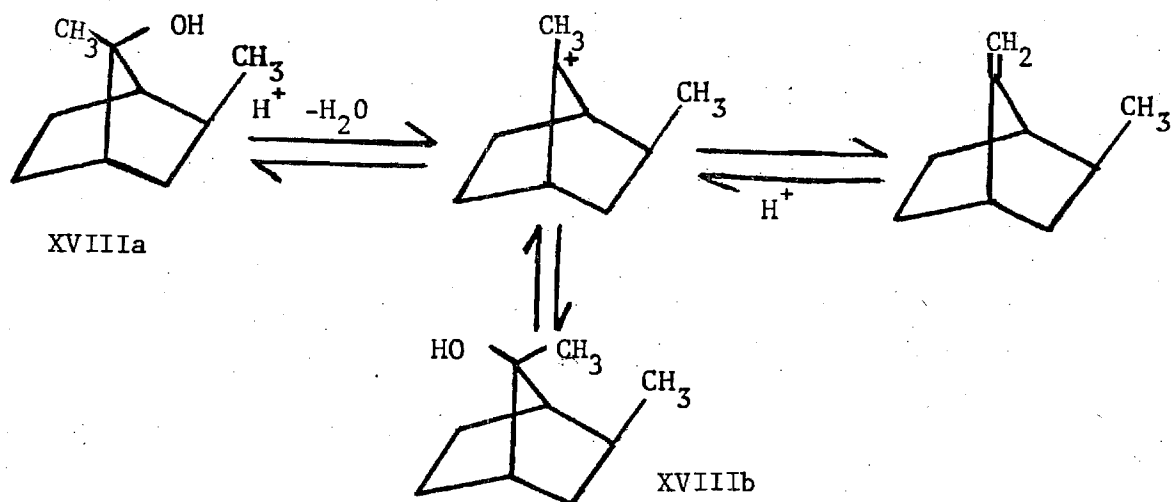
Alkylation of ketones (I), (II) and (III) were carried out using methylmagnesium bromide in diethyl ether in an attempt to evaluate the importance of "product development control" when ketones are allowed to react with organometallic alkylating agents. For a summary of these results see Table 5. Identification of the products of these reactions is essential just as in the case of the reduction study. The alkylation

of ketone (II) produced only one product as was verified by glc, ^1H NMR and ^{13}C NMR. Assuming that the lone alkylation product was the syn-alcohol, the anti-alcohol had to be synthesized. A straightforward method to produce the anti-alcohol was carried out according to Scheme 4. The first step in this sequence was to dehydrate the tertiary alcohol



Scheme 4: Proposed Synthetic Scheme for the Preparation of Exo-2-Methyl-7-Methyl-Anti-7-Norbornanol (XVIIIb).

to the methylene compound followed by epoxidation by meta-chloroperoxybenzoic acid which is then followed by LiAlH_4 reduction to yield the anti-alcohol. However, after periodic monitoring by glc, it was noted that a second peak appeared with a longer retention time than the starting "syn"-alcohol. This second peak continued to grow until it was approximately 1/3 of the starting reactant. This newly formed compound was separated by glc and identified by ^1H NMR and ^{13}C NMR. By comparing shielding parameters, as was done for the reduction products identification, this second compound was identified as the anti-alcohol. The following sequence is postulated to have taken place (Scheme 5). The first step in

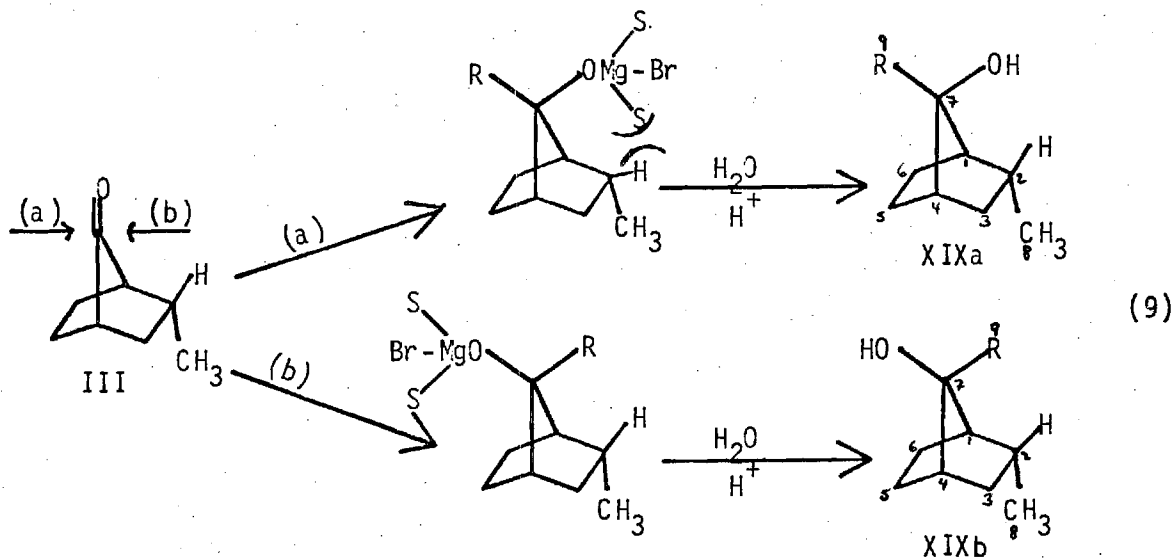
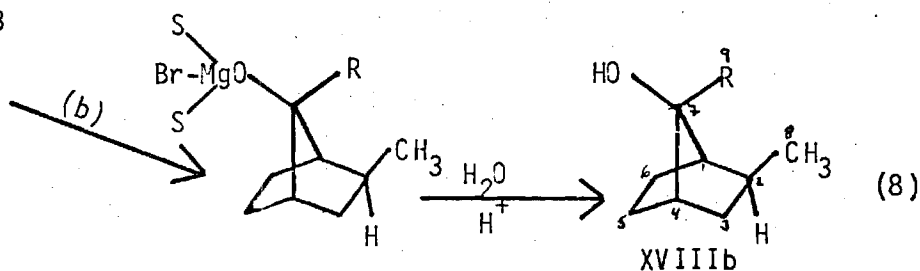
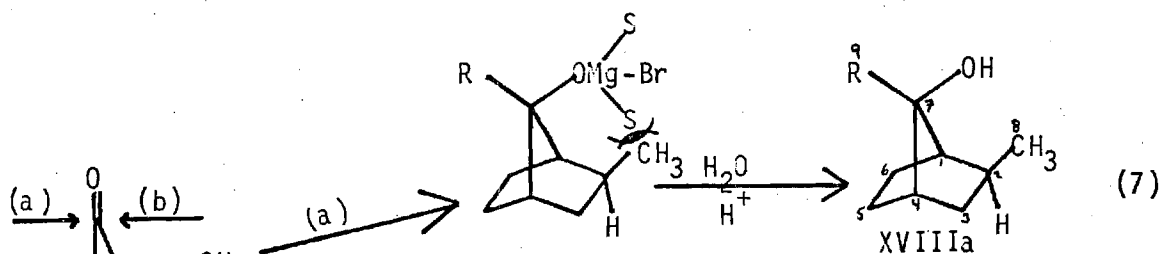
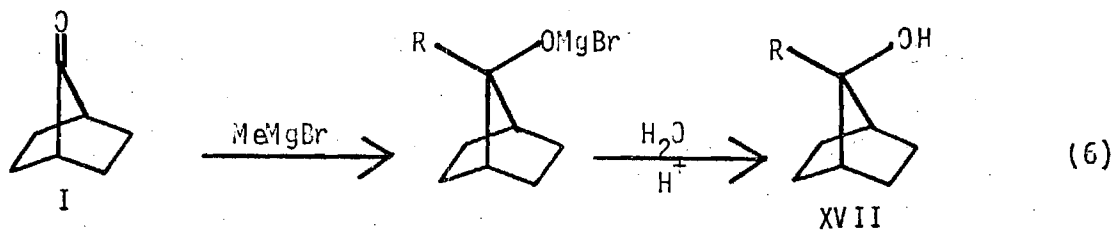


Scheme 5: Proposed Mechanism for the Acid Isomerization of (XVIIIa) to (XVIIIb).

the process is protonation of the alcohol with loss of water thus forming the carbonium ion. This can either lose a proton forming the methylene compound or pick up a hydroxyl group forming either the syn- or anti-alcohol since the total process is in equilibrium. Evidently the exo-2-methyl group has a steric requirement regarding the methyl group as well as the hydroxy group since the anti-alcohol is formed in only 33% compared to the syn-alcohol in equilibrium.

Stereochemistry of 7-Norbornanone Alkylation

The alkylation of ketone (I) (eq. 6), ketone (II) (eq. 7 and 8)



and ketone (III) (eq. 9) were carried out under identical conditions. As noted for the reduction reactions, only one alkylation product was obtained for ketones (I) and (II), whereas ketone (III) gave both the syn- and anti-alcohols according to glc, ^1H nmr and ^{13}C nmr. Table 5 shows the results of the alkylation studies with methylmagnesium bromide.

In Table 6 are recorded the observations of metal alkyl reactions with ketones (II) and (III). Both tables show essentially the same results as noted for the reductions studies conducted with the same ketones. That is, the exo-2-methyl group exerts a significant steric effect with respect to attack at the 7-keto group since no anti-alcohol is observed. Also, anti-attack on ketone (II) takes place at the same rate as attack from either side of the carbonyl on ketone (I) or (III) when in the presence of an insufficient amount of alkylating agent indicating that the exo-2-methyl group does not affect the formation of the syn-alcohol of ketone (II). Therefore it can be concluded that "product development control" in the alkylation reactions of this model ketone system is not important compared to "steric approach control".

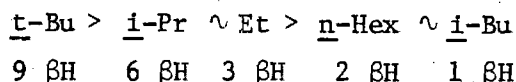
Reactions of Alkyl Grignard Reagents with Ketone (II)

Since the transition state formed on reaction of CH_3MgBr with exo-2-methyl-7-norbornanone (ketone II) should not exhibit torsional strain, compression effects and conformational changes, it is an ideal model ketone to evaluate "steric approach control" and "product development control". When CH_3MgBr was allowed to react with this ketone, only the syn-alcohol (XVa) was produced. For this reason, it was recently decided that exo-2-methyl-7-norbornanone (ketone II) might prove to be a useful

model for determining if a polar or SET mechanism or a combination of these is responsible for the products obtained from the reactions of Grignard reagents with ketones.

Due to the large steric effect associated with the exo-2-methyl group in ketone (II), a polar addition reaction should produce only the syn-alcohol (eq. 7). If a SET mechanism is in effect, a ketyl would first be formed, as in the Birch reduction (eq. 1), enabling both the syn- and anti-alcohols to form in 20:80 ratio when exo-2-methyl-7-norbornanone (II) was allowed to react with sodium in liquid ammonia. Therefore by allowing different Grignard reagents to react with ketone (II), observation of the alkylated anti-alcohol would indicate the possible participation of a SET mechanism.

Table 7 summarizes the results from a preliminary study of this postulation involving the reaction of ethyl, i-propyl, t-butyl, n-hexyl or i-butyl Grignard reagents with ketone (II). Unfortunately, in no case was any alkylated product observed. The major product in all cases was exo-2-methyl-syn-7-norbornanol (XVa). Small amounts of exo-2-methyl-anti-7-norbornanol (XVb) were also observed after quenching with water for all reactions except for the i-butyl Grignard reagent. The t-butyl Grignard reagent provided the greatest amount of (XVb) (11%). The other reagents produced 1-5% of (XVb). The following order of alkyl Grignard reagents was observed with respect to the formation of (XVb):



The reagent which has the most bulky β -alkyl groups had the least amount

of anti-alcohol (XVb) formed. Or in other words, the reagents with the most β -hydrogens produced the most anti-alcohol.

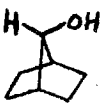
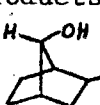
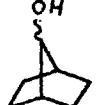
From the data, no conclusions can be made concerning polar or SET mechanisms, but reactions involving benzyl, phenyl, allyl, crotyl, vinyl etc., which could further our understanding of these mechanisms are now under further investigation.

CHAPTER IV

CONCLUSION

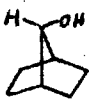
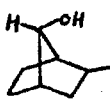
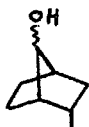
The concept of "product development control" has been used to explain the stereochemistry of many reactions in which the observed isomer ratio reflects the stability of the product. This concept has been used particularly to explain predominant formation of the most stable isomer in reactions of LiAlH_4 and MeMgBr with substituted cyclohexanones. A study of the reaction of LiAlH_4 and MeMgBr with 7-norbornanone and its exo-2-methyl and endo-2-methyl derivatives shows that the most unstable isomer is formed exclusively and hence "product development control" is not a factor in these reactions. In an attempt to broaden the scope of this study, three series of reagents were studied: (1) LiBH_4 , LiAlH_4 and LiGaH_4 , (2) BH_3 , AlH_3 and GaH_3 , and (3) $(\text{CH}_3)_2\text{Be}$, $(\text{CH}_3)_2\text{Zn}$, $(\text{CH}_3)_2\text{Mg}$ and $(\text{CH}_3)_3\text{Al}$. In no case was "product development control" observed. The reactions with the 7-norbornanone system are similar in nature to those with cyclohexanones, except that the complicating factors of torsional strain, compression effects and conformational changes which are present in cyclohexanone systems are not present in the 7-norbornanone system. The concept of "product development control" is, therefore, a questionable one in ketone reductions involving LiAlH_4 and alkylations involving MeMgBr .

Table 1. Reactions of LiAlH_4 with Ketones I, II and III in Diethyl Ether and THF.^a

Solvent	Ratio ^b Hydride:Ketone			Recovered ^c Ketone (%)			Products ^d			Mass Balance
	I	II	III	I	II	III	 (%)	 (%)	 (%)	
Et_2O	6.00	----	----	0.00	----	----	95	----	----	95
Et_2O	----	6.00	----	----	0.00	----	----	94	----	94
Et_2O	----	----	6.00	----	----	0.00	----	----	92	92
Et_2O	0.25	0.25	----	61	80	----	28	14	----	91
Et_2O	0.25	----	0.25	71	----	72	20	----	21	92
Et_2O	----	0.25	0.25	----	74	59	----	14	29	88
Et_2O	0.11	0.11	0.11	69	82	72	21	11	20	91
THF	----	6.00	----	----	0	----	----	94	----	94
THF	----	0.25	0.25	----	79	62	----	15	29	92
Et_2O	----	0.22	0.11	----	169	73	----	21	22	95
Et_2O	----	0.16	0.04	----	326	82	----	31	16	91
Et_2O	----	0.04	0.16	----	89	322	----	4	36	90

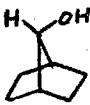
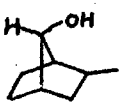

a) The hydride was added to 0.032 mmoles ketone at 25°C for 2 hrs. b) Hydride:Ketone = 6 is equivalent to LiAlH_4 :Ketone mole ratio of 1.5:1. c) % of each ketone recovered based on 100% relative to the amount of hydride added. d) % of each product based on 100% relative to the amount of hydride added.

Table 2. Reactions of Group IIIb Metal Hydrides with Ketones (II) and (III) in THF.^a

Reducing Agent	Ratio ^b Hydride:Ketone			Recovered ^c Ketone (%)			Products (%) ^d			Mass Balance
	I	II	III	I	II	III				
BH ₃	----	6.00	----	--	0	--	--	95	--	95
BH ₃	----	0.25	0.25	--	72	--	--	16	29	86
AlH ₃	----	6.00	----	--	0	--	--	96	--	96
AlH ₃	----	0.25	0.25	--	71	63	--	16	30	90
GaH ₃	----	6.00	----	--	0	--	--	95	--	95
GaH ₃	----	0.25	0.25	--	70	54	--	18	36	89

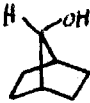
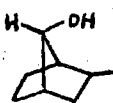

a) The hydride was added to 0.032 millimoles ketone at 25°C for 2 hours. b) Hydride:Ketone = 6 is equivalent to metal hydride:ketone mole ratio of 2:1. c) % of each ketone recovered based on 100% relative to the amount of hydride added. d) % of each product based on 100% relative to the amount of hydride added.

Table 3. Reactions of Common Cation Complex Metal Hydrides with Ketones (II) and (III) in THF.^a

Reducing Agent	Ratio ^b Hydride:Ketone			Recovered ^c Ketone (%)			Products (%) ^d			Mass Balance
	I	II	III	I	II	III				
LiBH ₄	----	6.00	----	--	0	--	--	97	--	97
LiBH ₄	----	0.25	0.25	--	74	60	--	16	32	91
LiAlH ₄	----	6.00	----	--	0	--	--	94	--	94
LiAlH ₄	----	0.25	0.25	--	79	62	--	15	29	92
LiGaH ₄	----	6.00	----	--	0	--	--	95	--	95
LiGaH ₄	----	0.25	0.25	--	75	59	--	13	26	86


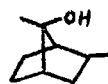
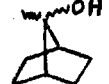
a) The hydride was added to 0.032 millimoles ketone at 25°C for 2 hours. b) Hydride:Ketone = 6 is equivalent to complex metal hydride:ketone mole ratio 1.5:1. c) % of each ketone recovered based on 100% relative to the amount of hydride added. d) % of each product based on 100% relative to the amount of hydride added.

Table 4. Reactions of Varying Cations of Complex Metal Hydrides with Ketones (II) and (III) in THF.^a

Reducing Agent	Ratio ^b Hydride:Ketone			Recovered ^c Ketone (%)			Products (%) ^d			Mass Balance
	I	II	III	I	II	III				
LiAlH ₄	----	6.00	----	--	0	--	--	94	--	94
LiAlH ₄	----	0.25	0.25	--	79	62	--	15	29	92
NaAlH ₄	----	6.00	----	--	0	--	--	96	--	96
NaAlH ₄	----	0.25	0.25	--	76	59	--	15	27	89
NR ₄ AlH ₄ ^e	----	6.00	----	--	0	--	--	95	--	95
NR ₄ AlH ₄ ^e	----	0.25	0.25	--	76	58	--	14	26	88


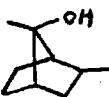
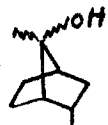
a) The hydride was added to 0.032 millimoles ketone at 25°C for 2 hours. b) Hydride:Ketone = 6 is equivalent to complex metal hydride:ketone mole ratio 1.5:1. c) % of each ketone recovered based on 100% relative to the amount of hydride added. d) % of each product based on 100% relative to the amount of hydride added. e) NR₄ = tri-n-octyl-n-propylammonium ion and the reagent was prepared in benzene.

Table 5. Methylmagnesium Bromide Reactions with Ketones (I), (II) and (III) in Diethyl Ether and THF.^a

Solvent	Ratio ^b Methyl:Ketone			Recovered ^c Ketone (%)			Products (%) ^d			Mass Balance
	I	II	III	I	II	III				
Et ₂ O	6.00	----	----	0	--	--	90	--	--	90
Et ₂ O	----	0.00	----	--	0	--	--	95	--	95
Et ₂ O	----	----	0.00	--	--	0	--	--	90	90
Et ₂ O	0.25	0.25	----	60	78	--	28	14	--	90
Et ₂ O	0.25	----	0.25	70	--	70	21	--	21	91
Et ₂ O	----	0.25	0.25	--	83	64	--	15	31	96
Et ₂ O	0.11	0.11	0.11	70	81	71	20	11	20	91
Et ₂ O	----	0.22	0.11	--	173	76	--	20	19	96
Et ₂ O	----	0.16	0.04	--	323	82	--	31	16	90
Et ₂ O	----	0.04	0.16	--	90	331	--	4	36	92
THF	----	6.00	----	--	0	--	--	93	--	93
THF	--	0.25	0.25	--	81	62	--	14	29	93

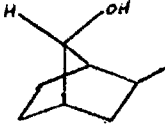
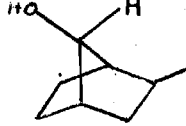
a) The alkylating agent was added to 0.032 millimoles ketone at 25°C for 1 hour. b) Methyl:Ketone = 6 is equivalent to RMgX:ketone mole ratio of 6:1. c) % of each ketone recovered based on 100% relative to the amount of alkylating agent added. d) % of each product based on 100% relative to the amount of alkylating agent added.

Table 6. Reactions of Alkylmetal Reagents with Ketones (II) and (III) in Diethyl Ether.^a

Alkylating Agent	Ratio ^b Methyl:Ketone			Recovered ^c Ketone (%)			Products (%) ^d			Mass Balance
	I	II	III	I	II	III				
Me ₂ Be	----	6.00	----	--	0	--	--	95	--	95
Me ₂ Be	----	0.25	0.25	--	83	64	--	15	31	97
Me ₂ Mg	----	6.00	----	--	0	--	--	95	--	95
Me ₂ Mg	----	0.25	0.25	--	81	60	--	17	33	96
Me ₂ Zn	----	6.00	----	--	0	--	--	67	--	67
Me ₂ Zn	----	0.25	0.25	--	65	43	--	11	20	70
Me ₃ Al	----	6.00	----	--	0	--	--	65	--	65
Me ₃ Al	----	0.25	0.25	--	60	41	--	10	20	65

a) The alkylating agent was added to 0.032mmoles ketone at 25°C for 1 hr. b) Methyl:Ketone = 6 is equivalent to R₂M:ketone mole ratio of 3:1. c) % of each ketone recovered based on 100% relative to the amount of alkylating agent added. d) % of each product based on 100% relative to the amount of agent added.

Table 7. Reactions of RMgX Compounds With Exo-2-Methyl-7-Norbornanone (II) in Et₂O Solvent at Room Temperature for 30 Hours in 2:1 Molar Ratio.^a

R	X	Recovered ^b Ketone (%)				
			Yield ^b of <u>Syn</u> - Alcohol (XVa) % (Rel%) ^c	% (Rel%) ^c	Yield ^b of <u>Anti</u> - Alcohol (XVb) % (Rel%) ^c	% (Rel%) ^c
Et	Br	35	44 (96)		2 (4)	
<u>i</u> -Pr	Br	4	88 (95)		5 (5)	
<u>t</u> -Bu	Cl	0	82 (89)		10 (11)	
<u>n</u> -Hex	Br	1	90 (99)		1 (1)	
<u>i</u> -Bu	Br	2	86 (100)		0 (0)	

a) The Grignard reagents were prepared by the standard methods. No products other than the reduction products were detected after quenching the reactions with a saturated solution of ammonium chloride. b) Yields were determined by glc and based on internal standards. c) Normalized % syn-alcohol + % anti-alcohol = 100%.

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PART II

HYDROMETALLATION OF ALKENES AND ALKYNES

CATALYZED BY TRANSITION METAL HALIDES

CHAPTER I

INTRODUCTION

Background

Considerable interest in organic synthesis at present is centered in the use of transition metal hydrides for the hydrometallation of alkenes and alkynes. Stoichiometric amounts of transition metal hydrides have been reported to reduce effectively unsaturated organic compounds. Conjugated C=C or C=N bonds¹⁻⁶ have been reduced and organic halides⁷ have been reductively dehalogenated by $[\text{HFe}(\text{CO})_4]^-$ and by several derivatives of "CuH".⁸⁻¹¹ In protic media¹² the same transformations can be accomplished by $[\text{HFe}_3(\text{CO})_{11}]^-$. Wailes and Schwartz have reported independently that hydrozirconation of alkenes¹³⁻¹⁵ and alkynes^{16,17} also involve a hydrometallation intermediate.

The hydrozirconation of alkenes was shown to proceed through the placement of the zirconium moiety at the sterically least hindered position of the alkene. The authors argued that the formation of the product involved either the regiospecific addition of Zr-H to a terminal alkene or Zr-H to an internal alkene followed by rapid rearrangement via Zr-H elimination and readdition to place the metal again in the least hindered position.

Transition metal hydrides are also used as catalysts for reactions of unsaturated hydrocarbons such as hydroformylation, hydrogenation, hydrosilation and isomerization.¹⁸ Recently, the reduction of alkenes and alkynes by the reagent LiAlH_4 -transition metal halide was reported.^{19,20}

Although one might assume that this reaction proceeds through a hydrometallation intermediate, deuterolysis of the reaction mixture shows that only titanium compounds are effective in the formation of the hydrometallation intermediate. Other first row transition metal compounds (e.g. NiCl_2 and CoCl_2) are effective in catalyzing the formation of reduction products although no evidence for a stable transition metal intermediate has been found.

Purpose

This research has centered around an investigation of the hydrometallation of alkenes and alkynes using less expensive and more readily available catalyst systems than has been used so far. The importance of forming the hydrometallated intermediate rather than the reduction product (alkane or alkene) lies in the formation of an organometallic compound that can be easily functionalized. Although hydroboration proceeds readily between an olefin and diborane in THF in the absence of a catalyst, the C-B bond is relatively stable and not as susceptible to functionalization as are C-Mg or C-Al compounds. Unfortunately, MgH_2 and AlH_3 do not hydrometallate alkenes or alkynes at all readily compared to B_2H_6 ; however, reaction does take place when certain transition metal halide catalysts are present.

CHAPTER II

EXPERIMENTAL SECTION

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.²² Calibrated syringes equipped with stainless steel needles were used for transfer of reagents. Glassware and syringes were flamed or heated in an oven and cooled under a flow of nitrogen or argon. All inorganic and organic compounds including 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. Proton NMR spectra were determined at 60 MHz with a Varian, Model A-60 or Model T-60 or at 100 MHz with a JOEL Fourier Transform spectrometer, Model PFT-100. The chemical shift values are expressed in ppm (δ values) 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 a 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. High pressure reactions were carried out in an autoclave rated to 15,000 psi obtained from the Superpressure Division of American Instrument Company of Silver Springs, Maryland.

Analytical

Gas analyses were carried out by hydrolyzing samples with 0.1 M hydrochloric acid on a standard vacuum line equipped with a Toepler pump.²³ 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).²⁴ The amount of active C-Li was determined by titrating the active reagent with dry 2-butanol in xylene using 2,2'-diquinoline as an indicator. Amine was analyzed by injecting hydrolyzed samples with an internal standard on the gas chromatograph. Carbon, hydrogen analyses were carried out by Atlanta Microlab, Inc., Atlanta, Georgia.

Analysis of all products arising from the quenching of reactions of alkenes and alkynes with hydride reagents with H_2O , D_2O , CO , CO_2 , I_2 , O_2 or carbonyl compounds were identified by glc and/or nmr and isolated by glc techniques and compared to authentic samples obtained commercially or synthesized by proven methods. All nmr spectra were obtained in CDCl_3 or benzene- d_6 using Me_4Si as the internal standard.

Materials

Solvents

Fisher reagent grade anhydrous diethyl ether was stored over sodium, then distilled under nitrogen from LiAlH_4 and/or sodium-benzophenone ketyl.

Fisher reagent grade tetrahydrofuran (THF) was dried over NaAlH_4 and distilled under nitrogen using diphenylmethane as a drying indicator.

Fisher reagent grade benzene and hexane 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 or argon.

Alkenes

1-Octene (b.p. $122-123^\circ\text{C}$), 1-methyl-1-cyclohexene (b.p. $110-111^\circ\text{C}$), styrene (b.p. $145-146^\circ\text{C}$), cis-2-hexene (b.p. $67-68^\circ\text{C}$), trans-2-hexene (b.p. $68-69^\circ\text{C}$), 1-hexene (b.p. $63-64^\circ\text{C}$), methylenecyclohexane (b.p. $102-103^\circ\text{C}$), 2-ethyl-1-hexene (b.p. $119-120^\circ\text{C}$), cyclohexene (b.p. $82-83^\circ\text{C}$), neohexene (b.p. $40-41^\circ\text{C}$), 2,3-dimethyl-2-butene (b.p. $72-73^\circ\text{C}$), and 2-methyl-2-butene (b.p. $35-38^\circ\text{C}$) were obtained from Chemical Samples Company or Aldrich Chemical Company and distilled and stored over 4 A molecular sieves.

Alkynes

1-Hexyne (b.p. $70-71^\circ\text{C}$), 2-hexyne (b.p. $83-84^\circ\text{C}$), 4-octyne (b.p. $132-133^\circ\text{C}$), 1-phenyl-1-propyne (b.p. $185-186^\circ\text{C}$), diphenylethyne (b.p. 170°C , 19 mm), and 1-octyne (b.p. $124-125^\circ\text{C}$) were obtained from Chemical Samples Company or Aldrich Chemical Company and distilled and stored over 4 A molecular sieves.

1-Trimethylsilyl-1-octyne. Into a 250 ml three-necked round bottom flask fitted with a Teflon coated magnetic stirring bar, rubber serum cap and a pressure equalizing addition funnel fitted with a three-way stop-cock connected to an argon filled manifold equipped with a mineral oil filled bubbler was placed 14.8 ml (11.0 g, 100 mmol) of 1-octyne in 50 ml of distilled hexane. To this stirred mixture, cooled with an ice-water bath, was slowly added 50 ml of 2.03 M n-butyllithium in hexane via syringe. After the addition, 30 ml of distilled hexane was added and

then the reaction mixture was allowed to warm to room temperature and stirred for three hours. The resulting white slurry was again cooled by an ice-water bath, and 13 ml (11.1 g, 112 mmols) of trimethylchlorosilane (distilled from quinoline) was slowly added over a period of $\frac{1}{2}$ hour. The resulting mixture was allowed to warm to room temperature and afterwards, stirred for three hours. Then 50 ml of water was added, slowly at first. The hexane layer was separated and washed twice with water, dried over anhydrous sodium sulfate and the solvent removed using a rotary evaporator. The crude product was distilled to give 15.1 g (0.083 mole, 83% yield) of 1-trimethylsilyl-1-octyne, b.p. 45-49°C (1.0-1.2 mm) (lit.²⁵ b.p. 49-50°C, 1.0 mm); IR(neat, film) 2950(s), 2860(s), 2180(s), 1470(m), 1250(s), 850(broad-s), 770(s), 710(m); NMR (CDCl₃, TMS) 9H singlet at 0.14 ppm, 3H multiplet at 0.68-1.06 ppm, 8H multiplet at 1.08-1.66 ppm, 2H multiplet at 2.00-2.38 ppm; mass spectrum, m/e (rel. intensity) 182(M⁺, 0.04), 168(18), 167(100), 154(3), 139(2), 123(3), 109(12), 96(13), 83(12), 73(26), 59(14).

Anal. Calcd for C₁₁H₂₂Si: C, 72.44; H, 12.16. Found: C, 72.23; H, 12.13.

Ketones and Aldehydes

Fisher Certified A.C.S. grade acetone was dried over MgSO₄, then filtered, distilled from P₂O₅ and stored over 4 Å molecular sieves.

Finton 4-t-butylcyclohexanone was sublimed under nitrogen.

Eastman benzophenone and Aldrich benzaldehyde were distilled under vacuum and stored under argon in the dark.

Preparation of Inorganic Reagents

Lithium aluminum hydride (Alfa Inorganics) solutions in THF or diethyl ether and sodium aluminum hydride (Alfa Inorganics) solutions in

THF were prepared by refluxing LiAlH_4 and NaAlH_4 in the appropriate solvent for at least 24 hours followed by filtration through a fritted glass filter funnel in the dry box. The clear solutions were standardized for aluminum content by EDTA and by hydrogen using standard vacuum line techniques.²⁰

Alane, AlH_3 , was prepared by the reaction of 100% H_2SO_4 with LiAlH_4 in THF at -78°C and filtered in the dry box²⁶ using a fritted glass filter funnel and dry Celite as a filter aid.

H_2AlCl , HALCl_2 , H_2AlBr , HALBr_2 and H_2AlI were prepared in THF by the redistribution reactions of AlH_3 and AlCl_3 , AlBr_3 or AlI_3 .²⁷ These reagents were characterized by analyzing for aluminum and hydrogen.

H_2AlOBu^t , $\text{HAL(Obu}^t)_2$, H_2AlOMe , HAL(OMe)_2 , $\text{H}_2\text{AlNPr}_2^i$, H_2AlNEt_2 , $\text{H}_2\text{AlN(SiMe}_3)_2$, $\text{HAL(NPr}_2^i)_2$, $\text{HAL(NEt}_2)_2$ and $\text{HAL[N(SiMe}_3)_2]_2$ were prepared by simply adding the appropriate alcohol or amine to AlH_3 in THF in a 1:1 or 1:2 molar ratio. Hydrogen was involved during the addition and the reaction was complete within 15 to 20 minutes except in the case of the reaction involving diisopropylamine or 1,1,1,3,3,3-hexamethyldisilazane in which case three hours of reaction time were required. The HALX_2 compounds were identified by their Al-H stretching frequency assignments:²⁸ $\text{HAL(Obu}^t)_2$, 1850 cm^{-1} ; HAL(OMe)_2 , 1840 cm^{-1} ; $\text{HAL(NPr}_2^i)_2$, 1810 cm^{-1} ; $\text{HAL(NEt}_2)_2$, 1820 cm^{-1} ; $\text{HAL[N(SiMe}_3)_2]_2$, 1800 cm^{-1} . These compounds were also analyzed for their aluminum content by titration with EDTA and back titration with zinc acetate and also by hydrogen analysis using standard vacuum line techniques.

These alkoxy and amino reagents were also prepared in benzene by removing the THF from the appropriate reagent under vacuum followed by

addition of freshly distilled benzene. This procedure was repeated three times until all THF had been removed. The solutions were then analyzed for aluminum and hydrogen content.

Activated LiH was prepared by the hydrogenation of t-butyllithium or n-butyllithium at 4000 psi for 12 hours at room temperature in hexane. The resulting LiH slurry was removed via syringe under an argon atmosphere or in a dry box.

Sodium hydride as a 50% oil dispersion was obtained from Alfa Inorganics. The oil was removed by repeated washing and decantations using freshly distilled hexane.

Lithium and sodium trimethylaluminumhydrides were prepared by the equal molar addition of a benzene, diethyl ether or THF solution of trimethylaluminum (obtained from Ethyl Corporation and distilled under vacuum in a dry box) to a lithium or sodium hydride slurry in the appropriate solvent. The addition was carried out in an appropriate sized one-necked round bottom flask equipped with a magnetic stirring bar and a pressure equalizing addition funnel while being cooled with an ice-water bath. The addition funnel was fitted with a rubber serum cap which was attached to an argon filled manifold connected to a mineral oil filled bubbler by a syringe needle. After the addition and stirring (usually 10 minutes) the reaction mixture became a clear, pale brown solution which was analyzed for aluminum by EDTA titration and lithium and sodium by flame photometry.

Sodium bis(2-methoxyethoxy) aluminum hydride (Vitride T) was obtained as a 70% toluene solution from Matheson, Coleman and Bell.

Lithium and sodium bis-diethylaminoaluminumhydride were prepared

either by adding with stirring at 0°C the stoichiometric amount of diethylamine to a THF solution of lithium or sodium aluminum hydride or by adding the stoichiometric amount of bis-diethylaminoalane (preparation discussed above) to activated lithium or sodium hydride. The clear, pale yellow-brown THF solutions were analyzed for lithium, aluminum and hydrogen by the standard methods described in the Analytical Section. If benzene solutions were desired, the THF was removed under vacuum and replaced by freshly distilled benzene. This procedure was repeated three times. The amount of THF according to glc which remained was $\leq 5\%$.

Bis-(cyclopentadienyl)-dimethyl Titanium

Into a 250 ml one-necked round bottom flask, equipped with a magnetic stirring bar and a pressure equalizing addition funnel fitted with a three-way stopcock with one arm connected to an argon filled manifold which in turn was connected to a mineral-oil filled bubbler, was placed 7.47 g (20.0 mmoles) of bis-(cyclopentadienyl)titanium dichloride, Cp_2TiCl_2 , and 100 ml of freshly distilled hexane. To this stirred and cold (-78°C) mixture was added 50 ml of 1.35 M MeLi in n-hexane (67.5 mmole) slowly over a 2 hour period. Then the mixture was allowed to warm to room temperature and stir for an additional two hours followed by slow addition of 2 ml of freshly distilled methanol. The organic layer was removed via syringe and the precipitate was washed repeatedly with distilled n-hexane. The hexane fractions were combined and stored in a freezer at -20°C . The solvent was removed from a 10 ml aliquot by flash evaporation. The resulting yellow-orange crystals melted at $96-97^\circ\text{C}$ (lit.²⁹ m.p. 97°C). The nmr spectra in benzene and TMS showed 5 H singlet at 5.71 ppm and 3 H singlet at 0.053 ppm.

Dicobalt Octacarbonyl

Because of the toxic nature of dicobalt octacarbonyl and cobalt tetracarbonyl hydride, all procedures^{30, 31} were conducted in a well ventilated hood.

Into a 500 ml stainless steel autoclave were placed 150 ml of hexane and 15 g of cobalt (II) carbonate (0.126 mole) obtained from Alfa Inorganics. The autoclave was flushed three times with carbon monoxide and then filled with an approximately equimolar mixture of hydrogen and carbon monoxide to a pressure of 3500 psi. The autoclave was heated with agitation to 150°C and these conditions were maintained for three hours. The autoclave was then cooled to room temperature, the gases vented slowly and the autoclave opened in a well ventilated hood.

The clear dark solution of dicobalt octacarbonyl was pipetted from the autoclave via syringe and filtered through a fritted glass filter. The filtrate was then stored over night in a freezer (-20°C) during which time large, purple crystals were formed. The solvent was decanted and the crystals were dried using a stream of dry carbon monoxide. The dry crystals (16.5 g, 78%) melted with some decomposition at 50-51°C (lit.³⁰ m.p. 51-52°C). The product was stored under a carbon monoxide atmosphere.

Cobalt Tetracarbonyl Hydride (Cobalt Hydrocarbonyl)

A 500 ml three-necked round bottom flask was equipped with a pressure-equalizing addition funnel fitted with a rubber serum cap, an inlet tube which was constricted at the tip to about 2 mm and inserted nearly to the bottom of the flask, and a three-way stopcock with one arm attached to a 36 mm X 110 mm drying tube containing a mixture of P₂O₅

and glass beads. This apparatus in turn was attached to a cold trap immersed in liquid nitrogen and with its outlet tube connected to a mineral oil filled bubbler.

Three grams of cobalt octacarbonyl (0.009 mole) were placed into a 300 ml ground glass Erlenmeyer flask. Twenty ml of freshly distilled pyridine (0.248 mole) was added and the flask attached to a mercury filled bubbler to prevent entry of air and to monitor the formation of carbon monoxide which was complete in a couple of minutes. The resulting solution was added to the addition funnel. A solution of 25 ml of conc. H_2SO_4 and 75 ml of water was cooled to $0-5^\circ\text{C}$ and added to the round-bottom flask cooled by an ice-water bath. Before the pyridine solution was added, the apparatus was purged with carbon monoxide at a flow of about 300 cc/min. The slow addition was performed over 1 hour. The flask was then purged with carbon monoxide for another 15 minutes which allowed the cobalt hydrocarbonyl to be transferred from the reaction flask to the cold trap. After the carbon monoxide was allowed to evaporate slowly leaving behind the $\text{HCo}(\text{CO})_4$, about 2 g (95%) of product was isolated in this manner. Hexane solutions were prepared by the addition of freshly distilled hexane and stored at -78°C over sodium sulfate. Analysis of the above solutions was by the method of Orchin, et al.³² which incorporated the titration of the cobalt hydrocarbonyl by tris-(1,10-phenanthroline) nickel (II) chloride. The analysis was also carried out in the following manner: Into a 50 ml Erlenmeyer flask is placed a Teflon stirring bar, 10 ml of water and several drops of ethanolic phenolphthalein. The flask is fitted with a rubber serum cap and then purged with carbon monoxide through syringe needles. A 1 ml sample of

the hexane solution is added. The resulting two-phase system is then stirred continuously during titration with 0.01 N sodium hydroxide.

Metal Salts

AlCl_3 , AlBr_3 and AlI_3 (Alfa Inorganics) were sublimed just prior to use and crushed to a fine powder in the dry box.

The following transition metal halides were obtained from Fisher: TiCl_3 , TiCl_4 , CrCl_3 , MnCl_2 and ZnBr_2 . Alfa Inorganics supplied the following transition metal halides: VCl_3 , FeCl_3 , FeCl_2 , CoCl_2 , NiCl_2 , Cp_2TiCl_2 , Cp_2ZrCl_2 , $\text{Cp}_2\text{Ni}(\text{PPh}_3)\text{Cl}$, $\text{Ni}(\text{acac})_2$, $\text{Ni}(\text{PPh}_3)_2\text{Br}_2$, allyl- $\text{Ni}(\text{dpe})\text{Br}$, Cp_2VCl_2 and the polymer bound benzyl titanocene dichloride (Grubb's catalyst). All transition metal halides were opened only in the dry box and used without further purification.

General Reactions of Alkenes and Alkynes

A 10 X 18 mm test tube with a Teflon coated magnetic stirring bar was flamed and cooled under a flow of argon or nitrogen. Transition metal halide (5 mole % in most cases) was transferred to a tared test tube in the dry box. The flask was sealed with a rubber serum cap, removed from the dry box, reweighed and connected by means of a syringe needle to a nitrogen or argon-filled manifold equipped with a mineral oil-filled bubbler. However, in the case of Cp_2TiCl_2 , a saturated solution in benzene (0.02 M) or THF (0.125 M) was prepared; however, the solutions had to be made fresh each day. One or two ml of THF or benzene was introduced into the reaction vessel and then the olefin or alkyne added. The mixture was stirred for 2 to 3 minutes before the reagent was added. The the reaction mixture was stirred at room temperature or at higher temperatures, depending upon the reactants, for up to 40 hours in some

cases. In general the reaction between the terminal alkenes and internal alkynes were complete in 20 minutes. The reactions were quenched by various means (see below-General Quenching Techniques) and worked up by the regular method (addition of water, extraction with THF, diethyl ether or hexane and drying over MgSO_4). Most products were separated by glc using a 6 ft. 10% Apiezon L 60-80 column with a helium flow rate of 45 ml/min: 1-octene (110°C , oven temperature), 1-methyl-1-cyclohexene (50°C), 2-ethyl-1-hexene (50°C), cyclohexene (50°C); a 20 ft. 10% TCEP column with a helium flow rate of 45 ml/min for 1-hexene, cis-2-hexene, trans-2-hexene, neohexene, 2-methyl-2-butene and 2,3-dimethyl-2-butene (45°C , flow rate 25 ml/min); 2-hexyne, 1-octyne and 1-hexyne (70°C , flow rate 45 ml/min); 1-trimethylsilyl-1-octyne (100°C , flow rate 45 ml/min); 1-phenylpropyne (125°C , flow rate 45 ml/min); a 10 ft. 5 % carbowax 20 M column for diphenylethyne (200°C , flow rate 60 ml/min). The yield was calculated by using a suitable hydrocarbon internal standard for each case ($\text{n-C}_{12}\text{H}_{26}$, $\text{n-C}_{14}\text{H}_{30}$ or $\text{n-C}_{16}\text{H}_{34}$) and the products were identified by comparing the retention times of authentic samples with the products under similar conditions and/or by coinjection of products and authentic samples obtained commercially or synthesized by proven methods.

Yields of cis-stilbene (δ 6.60, vinyl H), trans-stilbene (δ 7.10, vinyl H) and 1,2-diphenylethane (δ 2.92 benzyl H) were determined by NMR integration and based on total phenyl protons. However, the ratio of cis-stilbene to trans-stilbene was also checked by glpc.

General Quenching Techniques

Quenching with H_2O . After the desired reaction time for the catalytic hydrometallation reaction described above, the reaction was

quenched with water or a saturated solution of ammonium chloride to produce the protonated species. The amount of recovered starting material (alkene or alkyne) and products were determined by the methods described above.

Quenching with D₂O. The same procedure used for quenching with H₂O was followed. The amount of recovered starting material and products were determined by glc methods and conditions described above. Each product was collected from the gas chromatograph and submitted for mass spectrum analyses. The corrected percent of deuterium incorporation for the product was calculated by comparing the protonated species' mass spectrum with the deuterated species' mass spectrum and by subtracting the contributions of naturally occurring isotopic components from each molecular ion peak. This procedure was followed for all unsaturated substrates observed under these reaction conditions.

The regioselectivity of reactions was monitored by use of NMR for styrene, 1-phenyl-1-propyne and 1-trimethylsilyl-1-octyne. In the case of styrene, 98% of the product, ethylbenzene, was deuterated with 90% of the deuterium located on the α carbon as indicated by a quartet at 2.64 ppm (2H) $J = 8$ Hz and a doublet (3H) at 1.23 ppm, $J = 8$ Hz.

For 1-phenyl-1-propyne, 95% of the product, cis-1-phenylpropene, was deuterated with 90% of the deuterium located on the number 1 carbon as indicated by a quartet of triplets at 5.78 ppm, $J = 7$ Hz (1H) and a doublet at 1.89 ppm, $J = 7$ Hz (3H). The other isomer showed a singlet at 1.89 ppm and a multiplet at 6.36-6.54 ppm. It was identified as trans-1-phenylpropene.

The products from the reduction of 1-trimethylsilyl-1-octyne were

prepared independently. Cis-1-trimethylsilyl-1-octene was prepared from the hydrogenation of 1-trimethylsilyl-1-octyne with 5% Pd/C used as the catalyst and 95% ethanol used as the solvent and monitored until the desired amount of hydrogen was absorbed. The cis-isomer was collected and purified via glpc under the aforementioned conditions. The trans-isomer was also detected by glpc. The cis-isomer when coinjected under glc conditions with the product of the hydroalumination reaction, showed a trace characteristic of only the cis-isomer. The trans-isomer obtained from the hydrogenation reaction had an identical retention time as the minor product from the hydroalumination reaction.

The following data were obtained for cis-1-trimethylsilyl-1-octene: IR (neat, film) 2960(s), 2940(s), 2860(m), 1600(m), 1470(m), 1260(s), 850 (broad-s); NMR (CCl_4 , TMS) 9H singlet at 0.14 ppm, 11H multiplet at 0.74-2.66 ppm, 2H quartet at 2.15 ppm, $J = 8$ Hz, 1H doublet at 5.49 ppm, $J = 13.0$ Hz, 1H doublet of triplets at 6.33 ppm, $J = 14$ Hz and 7 Hz; mass spectrum, m/e (rel. intensity) 184(M^+ , 2), 170(13), 169(70), 141(4), 125(4), 114(23), 109(13), 99(26), *5(15), 73(100), 67(9), 59(91), 44(21), 41(14).

Anal. Calcd for $\text{C}_{11}\text{H}_{24}\text{Si}$: C, 71.65; H, 13.12. Found: C, 71.54; H, 13.14.

The nmr spectrum of the trans-isomer matched the spectrum found in the literature:³³ NMR (CCl_4 , TMS) 9H singlet at 0.16 ppm, 11H multiplet at 0.6-1.6ppm, 2H multiplet at 2.1 ppm, 1H doublet at 5.6 ppm, $J = 18 \text{ Hz}$, 1H doublet of triplets at 6.0 ppm, $J = 18 \text{ Hz}$ and 6 Hz .

When 1-trimethylsilyl-1-octyne was allowed to react under the catalyzed hydrometallation conditions described above, 87% of the product, cis-1-trimethylsilyl-1-octene, was deuterated and approximately 90% of

the deuterium was located on carbon number 2, as indicated by the following: NMR (CDCl_3 , TMS) 9H singlet at 0.14 ppm, 11H multiplet at 0.80-1.56 ppm, 2H broad singlet at 2.14 ppm, 1H singlet at 5.49 ppm. The other isomer (trans-1-trimethylsilyl-1-octene) had no deuterium incorporation but showed a triplet at 6.33 ppm which corresponded to the expected splitting pattern of the non-deuterated trans-isomer.

Quenching with I_2 . A known concentration of iodine in benzene was prepared and a stoichiometric amount was added to the catalytic hydroalumination reaction after the desired time. This mixture was then allowed to stir at room temperature for 1 hour. Afterwards, water was added followed by a saturated sodium thiosulfate solution. The organic layer was then separated and dried over sodium sulfate and analyzed by glc or NMR. This procedure was followed for the following substrates: 1-octene, 1-hexene, cis-2-hexene, trans-2-hexene, 3-hexene and 2-hexyne. The iodoalkane-compounds prepared in this manner were confirmed by comparison of authentic samples purchased from Eastman Chemical Company or by quenching the corresponding alkyl Grignard with iodine and worked up in the aforementioned manner. The iodoalkenes were identified by NMR and discussed below.

When the catalytic hydroalumination reactions of internal alkynes were quenched with D_2O , the products are the cis-alkenes which were confirmed by coinjection of authentic samples on the gas chromatograph. From Zweifel's³⁴ work, it was reported that hydroaluminated compounds quenched with iodine maintain their regiochemistry. Therefore the iodoalkene obtained from the quenching of the 2-hexynyl reaction with iodine produced 2- and 3-iodo-cis-2-hexene. NMR was used to distinguish

between the two isomers: $\begin{array}{c} \text{H} & & \text{I} \\ & \diagdown & / \\ & \text{C}=\text{C} \\ & / & \diagdown \\ \text{L} & & \text{R} \\ | & & | \\ \text{C} & & \text{CH}_3 \\ / & & \\ \text{R} & & \end{array}$ (CH_3 singlet at 2.36 ppm) and $\begin{array}{c} \text{H} \\ | \\ \text{C} \\ | \\ \text{R} \\ | \\ \text{CH}_3 \end{array}$ (CH_3 doublet at 1.63 ppm $J = 7 \text{ Hz}$). The following spectra were also obtained: IR(neat, film) 2940(s), 2920(s), 2850(m), 1625(m), 1460(s), 1430(s), 1380(s), 1120(s), 1070(m), 1055(m), 1040(m); mass spectrum, m/e (rel. intensity) 210(M^+ , 100), 181(10), 168(3), 128(4), 127(6), 83(19), 67(6), 55(91), 41(3).

Anal. Calcd for $\text{C}_6\text{H}_{11}\text{I}$: C, 34.30; H, 5.28. Found: C, 34.51; H, 5.25.

Quenching With Carbonyl Compounds. After the desired catalytic hydroalumination reaction had taken place, a stoichiometric amount of desired carbonyl compound (acetone and benzaldehyde) was added, followed by additional stirring for 10 hours accompanied by maintaining the desired temperature with an oil bath. The reaction mixtures were then worked up by addition of water. The organic layer was then separated, dried over MgSO_4 , filtered and analyzed by NMR techniques.

One of the products arising from the quenching of 1-octene and 4-octyne reactions with acetone, the reduction product, isopropanol, was determined by observation of the methyl group attached to the carbinol carbon (doublet at 1.2 ppm). Acetone was determined by observation of the methyl groups attached to the carbonyl carbon (2.05 ppm). 1-Octene was identified by the vinyl proton multiplet at 4.8–5.2 ppm (2H) and 5.52–6.24 ppm (1H). 4-Octyne was identified by the triplet corresponding to the methyl group at 0.98 ppm. 1-Octene and 4-Octyne were also determined by glc analyses. The addition products were determined by nmr observation of the methyl groups which appeared as singlets at 1.22 ppm and by comparing these spectra with those obtained from the reaction of

corresponding octyl Grignard reagents with acetone. The integrity of the octenyl addition compound was established by the methyl singlet at 1.22 ppm and the appearance of a multiplet at 5.5-6.3 ppm.

For the products arising from the quenching of 1-octene and 4-octyne reactions with benzaldehyde, benzaldehyde was determined by the singlet associated with the aldehydic proton at 9.94 ppm, the reduction product, benzyl alcohol, was determined by the singlet found at 4.58 ppm, the addition product from 1-octene was determined by the methine proton triplet at 4.60 ppm corresponding to the Grignard addition product's nmr spectrum and the addition product from 4-octyne was determined by the appearance of the vinyl multiplet at 5.5-6.3 ppm and also by glc, mass spectral and ir analyses.

When $\text{HAL}(\text{NPr}_2^1)_2$ was allowed to react with 1-octene or 4-octyne in the presence of 2 mole % Cp_2TiCl_2 and then allowed to react with benzaldehyde, the major product was diisopropylbenzylamine in both cases. The following data were obtained: n_D^{25} 1.5300; NMR (CDCl_3 , TMS) 12H doublet at 1.01 ppm, $J = 5 \text{ Hz}$; 2H multiplet at 2.66-3.34 ppm; 2H singlet at 3.63 ppm; 5H multiplet at 7.10-7.40 ppm; mass spectrum, m/e (rel. intensity) 191(M^+ , 8), 176(56), 134(5), 132(3), 114(2), 106(6), 105(6), 91(100), 84(2), 77(6), 65(6), 51(3), 43(5), 42(4), 41(5), 39(3); IR (neat, film) 3090(w), 3070(w), 3030(m), 2970(s), 2940(m), 2880(w), 1605(m), 1495(m), 1470(m), 1455(m), 1385(s), 1375(s), 1210(s), 1180(s), 1155(m), 1140(m), 1120(m), 1075(w), 1050(w), 1025(s).

Anal. Calcd for $\text{C}_{13}\text{H}_{21}\text{N}$: C, 81.61; H, 11.07. Found: C, 81.49; H, 11.00.

When $\text{HAl}(\text{NEt}_2)_2$ was allowed to react under similar conditions, the major product was diethylbenzylamine: n_{D}^{25} 1.5325; NMR (CDCl_3 , TMS) 6H triplet at 1.07 ppm, $J=6 \text{ Hz}$; 4H quartet at 2.42 ppm, $J=6 \text{ Hz}$; 2H singlet at 3.64 ppm, 5H multiplet at 7.10–7.40 ppm; mass spectrum, m/e (rel. intensity) 163(M^+ , 6) 148(19), 133(6), 132(7), 118(7), 109(11), 108(25), 107(19), 106(79), 105(83), 91(68), 86(7), 80(11), 79(21), 78(22), 77(100), 65(8), 58(18), 51(42), 45(18), 43(26), 39(14); IR (neat, film) 3090(w), 3070(w), 3030(w), 2970(s), 2940(m), 2880(w), 1605(m), 1495(m), 1470(m), 1450(m), 1380(s), 1215(s), 1185(s), 1145(m), 1120(s), 1070(m), 1030(s), 950(s).

Anal. Calcd for $\text{C}_{11}\text{H}_{17}\text{N}$: C, 80.92; H, 10.50. Found: C, 81.05; H, 10.45.

General Reactions of Complex Metal Hydrides

The same general procedure used for the bis-dialkylaminoalane reactions of alkenes and alkynes were followed as described above. The complex metal hydrides used were lithium and sodium aluminum hydride, sodium bis-(2-methoxyethoxy) aluminum hydride and lithium and sodium trimethylaluminum hydride. The reactions were quenched with H_2O , saturated solution of ammonium chloride, D_2O or a benzene solution of iodine and worked up as described above. The products were identified by the above procedures.

General Reactions of LiH or NaH

The same procedure for the catalytic hydroalumination reactions of alkenes and alkynes with bis-dialkylaminoalanes described above were also followed for this part of the investigation. The identification of the products proceeded as before by glc analyses and by comparison with authentic samples.

General Reactions for the Carbonylation of Simple and Mixed Metal Hydrides

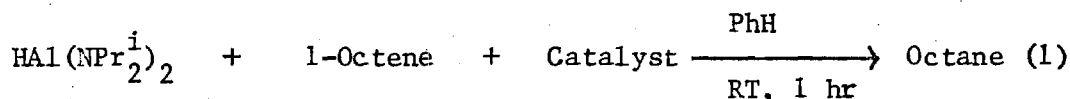
The simple and complex metal hydrides were carbonylated at 4000 psi using a high pressure apparatus at room temperature. Diethyl ether, THF or hexane was used as the solvent and the reactions were carried out over a 24 hour period. Gas-liquid chromatography was used to confirm the production of methanol, ethanol and/or methyl formate by comparison with authentic samples.

CHAPTER III

RESULTS AND DISCUSSION

Reactions of Alkenes

The monosubstituted olefin, 1-octene, was chosen as a representative olefin for the initial evaluation of catalysts in the study of hydroalumination of olefins. Bis-diisopropylaminoalane, $[\text{HAL}(\text{NPr}_2^i)_2]$, was chosen as a representative alane and was allowed to react with 1-octene in the presence of 5 mole percent of various transition metal compounds (eq. 1). Nearly quantitative yields of octane were obtained



when TiCl_3 , TiCl_4 , CoCl_2 , NiCl_2 , Cp_2TiCl_2 , polymer bound benzyltitanocene dichloride, $\text{CpNi}(\text{Ph}_3\text{P})\text{Cl}$, $\text{Ni}(\text{PET}_3)_2\text{Br}_2$ and allyl-Ni(dep)Br were used as catalysts (Table 8). The intermediate formation of the octyl aluminum compound was monitored by the percent deuterium incorporation observed when the reaction was quenched with D_2O . Even though the yields of octane were high, only the titanium catalysts provided high yields of products showing deuterium incorporation. The best catalyst for this reaction (eq. 1) appears to be titanocene dichloride, Cp_2TiCl_2 .

Scheme 6 outlines the proposed mechanism involved in the catalytic hydrometallation process. The transition metal halide is proposed to react with the disubstituted alane to produce the disubstituted chloro-aluminum compound and the transition metal hydride. The hydroalumination species is presumed to be the transition metal hydride and the reducing



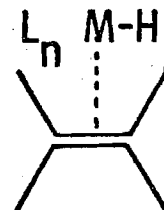
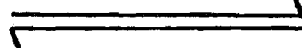
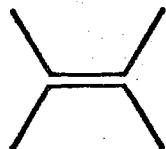
M = Transition Metal

X = OR, NR₂, Cl

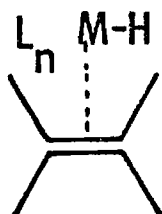
L = Halogen, Cp



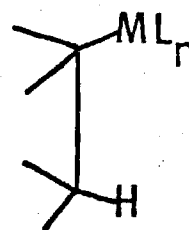
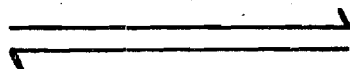
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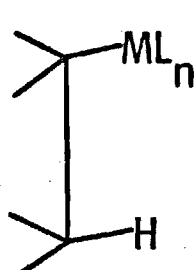
A



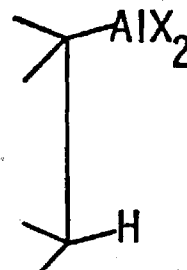
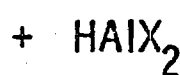
A



B



+



+



ALKANE

Scheme 6: Proposed Catalytic Hydrometallation Mechanism.

ability of the reagent is believed to be due to d-orbital overlap between the metal ion and the unsaturated carbon-carbon bond. Under this assumption, $\text{Cu}^{\text{I}}(\text{d}^{10})$ and $\text{Zn}^{\text{II}}(\text{d}^{10})$ have no empty d-orbitals to overlap with the olefin, and $\text{Mn}^{\text{II}}(\text{d}^5)$ with the d-orbitals half filled would be predicted to have a lower activating ability. Under the conditions described above, Cu, Zn and Mn catalysts are considerably slower reacting than the titanium cobalt or nickel catalysts. This explanation is consistent with the results obtained.

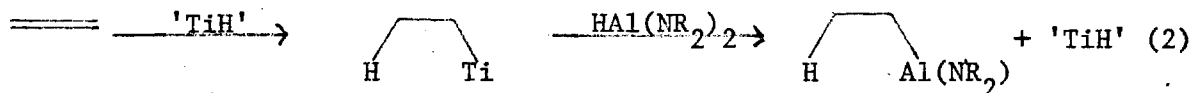
After the addition of all the reactants and reagents, a blue-violet color appeared which represented the formation of the transition metal hydride.³⁵ As stated above, Cp_2TiCl_2 was shown to be an effective catalyst;³⁶ however, when Cp_2TiMe_2 was employed as the catalyst, no color change was observed and none of the anticipated products was formed and the starting material was recovered. This can be explained by the fact that the chloride in titanocene dichloride is a better leaving group than the methyl group in dimethyltitanocene and therefore Cp_2TiCl_2 is more acceptable as a catalyst involving simple displacement by the bis-dialkylaminoalanes than Cp_2TiMe_2 .³⁷ The transition metal hydride first coordinates with the unsaturated substrate forming complex A.

The next step involves β -hydride addition of the transition metal hydride to the coordinated unsaturated substrate forming compound B. Hoffman³⁸ proposed that this equilibrium depends on the donation of the electron density on the metal thus stabilizing the olefin complex. Therefore by using a d^0 metal (e.g. $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$), specific activation of the alkene or alkyne should be accomplished; in other words, the d^0 metal-alkyl complex B should predominate over the unsaturated complex A

at equilibrium. Once the alkyl transition metal compound is formed, a transmetallation step with the disubstituted alkane takes place. Hart and Schwartz³⁹ have shown that alkyl groups can be transferred from zirconium to aluminum simply by treatment with AlCl_3 . It is suggested that a similar process occurs in the analogous titanium system. The transition metal hydride complex which is also formed in this step can now react with more substrate to continue the hydrometallation process.

In order to determine the nature of the reaction intermediate when alkene is allowed to react with $\text{HAL}(\text{NR}_2)_2$ in the presence of transition metal halides, deuterium incorporation experiments were carried out by quenching the reaction mixtures with deuterium oxide. The products were collected by preparative glc and the deuterium content (%) was measured by the molecular ion peak ratio of deuteriated and non-deuterated product in the mass spectrum. These results are also listed in Table 8. The only experiments giving high yields of product and deuterium incorporation occurred with the titanium catalysts (TiCl_3 , 65%; TiCl_4 , 80% and Cp_2TiCl_2 , 93%). A notable exception was the polymer bound benzyltitanocene dichloride (Grubb's Catalyst). The catalyst produced 99% of the reduced alkene but no deuterium was incorporated when the reaction was quenched with D_2O . It was hoped that with a polymer bound catalyst, the hydrometallated species could easily be removed from the catalyst thereby reducing the probability of further side reactions taking place. These results imply that the hydrometallated transition metal halide intermediate is not stable under the conditions studied except for the titanium catalysts. In other words, the transmetallation reaction involving alkyl transfer from the transition metal to aluminum

proceeds only for the reactions with titanium catalysts (eq. 2).



Several experiments were carried out in an attempt to stabilize the carbon-transition metal bond by varying the ligands attached to the transition metal. It is expected that ligands are capable of stabilizing the transition metal compounds by dispersing the d-orbitals of the transition metal through the attached ligands. The addition of triphenyl- or triethylphosphine to nickel chloride did not have much of an effect on the percent deuterium incorporation. However, the addition of cyclopentadienyl ligands to TiCl_4 had pronounced effect on deuterium incorporation (93%).

It was also shown that the amount of deuterium incorporation increased when the solvent was changed from THF (78%) to benzene (88%) and when the atmosphere was changed from nitrogen (88%) to argon (93%) (Table 9). The changing of a nitrogen atmosphere to one of argon increased the amount of deuterium incorporation observed because evidently N_2 was "fixed" to the titanium atom in a side reaction. The changing of solvents from THF to benzene also increased the amount of deuterium incorporation presumably due to the inability of benzene to donate a hydrogen atom during homolytic cleavage of the R-Ti compound as would be the case for THF.

Table 10 contains the observed results from reaction of a series of alkenes with $\text{HAL}(\text{NPr}_2)_2$ in the presence of 5 mole percent Cp_2TiCl_2 . All

of the reactions were conducted in benzene at 60°C for 12 hours except that for the 1-octene experiment which was over in 10 minutes at room temperature. Relative rates for these reactions were found to be styrene ~ 1-octene > 3,3-dimethyl-1-butene > methylene cyclohexane > 2-ethyl-1-hexene >> cis-2-hexene ~ trans-2-hexene >> cyclohexene >>> 2-methyl-2-butene ~ 2,3-dimethyl-2-butene ~ 1-methylcyclohexene. These rates parallel the rates found by Schwartz for the hydrozirconation reactions.¹⁵

The percent deuterium incorporation, which monitored the production of the intermediate alkyl aluminum compounds, was high for styrene, 1-octene, cis-2-hexene, trans-2-hexene, methylene cyclohexane and 2-ethyl-1-hexene (98, 93, 83, 81, 72 and 75% respectively). The notable exception was 3,3-dimethyl-1-butene which gave a high yield of 2,2-dimethylbutane, reduction product, in this case 2,2-dimethylbutane, was obtained (99%), but only 10% deuterium incorporation of the product was observed. Cyclohexene and the trisubstituted or tetrasubstituted olefins, 1-methylcyclohexene, 2-methyl-2-butene or 2,3-dimethyl-2-butene, provided only small or no amounts of the corresponding alkanes. This implies that the greater the steric bulk of the olefin the slower the reaction.

According to Scheme 6, the critical step in the catalytic hydrometallation reaction is the production of A which leads to the formation of B in a regioselective manner where the transition metal proceeds to the terminal carbon for primarily steric reasons. This result is substantiated by the fact that only 1-iodooctane is produced when the catalytic hydrometallation reaction product of 1-octene is quenched with iodine (Table 11). When 2-ethyl-1-hexene is the substrate, the transition metal hydride complex can arrange itself in a manner where the compression

effect is minimal (Figure 1). This allows the normal reaction to proceed

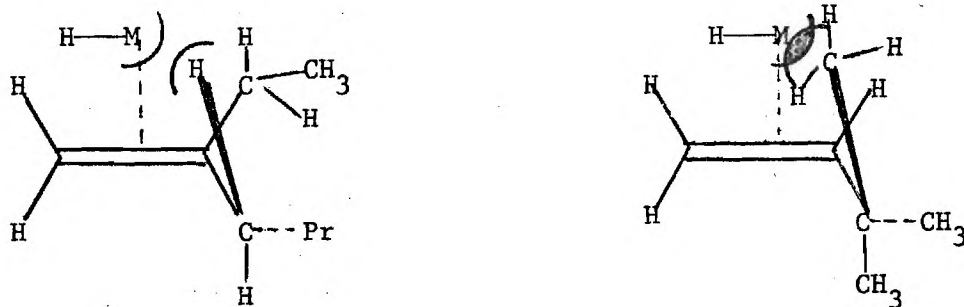


Figure 1

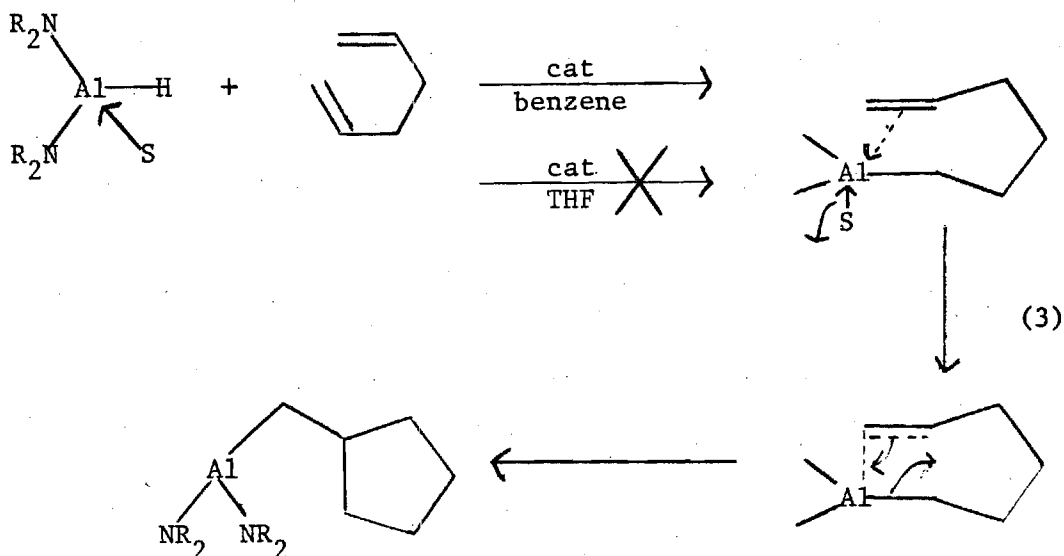
and hence a large percentage of deuterium incorporation. But for the neohexene reaction, the now present methyl group exerts a larger compression effect than the hydrogen in the 2-ethyl-1-hexene system. This, therefore, prevents the proper alignment of the groups and forces the reaction to follow a different pathway and consequently, no deuterium incorporation is observed in the product.

It should also be noted that 98% of ethylbenzene produced from the styrene reaction was incorporated with deuterium after quenching with D_2O . Of that 98%, 90% of the deuterium was located in the 1 position, $PhCH(D)CH_3$. As will be discussed latter, the titanium hydrido-chloride catalyst could complex with the π cloud of the phenyl ring (Scheme 7, complex A_1) permitting the titanium to be close to the carbon holding the phenyl ring. This phenomenon will once again be evident for the 1-phenylpropyne reaction.

When 1-hexene, 1-octene, cis-2-hexene and trans-2-hexene are allowed to react under conditions listed above, but quenched with iodine, only the corresponding 1-iodo-compounds were produced (Table 11). This observation is consistent with previous findings of Schwartz observed for the hydrozirconation process.¹⁵ It has been shown that zirconium (IV) and titanium (IV) salts can catalyze the isomerization of secondary aluminum reagents⁴⁰ to produce primary aluminum reagents. These isomerizations may occur through reversibly β -hydride elimination and re-addition mechanisms mentioned before in reference to Scheme 6.

Reactions of Dienes

When dienes (Table 12) were allowed to react under these conditions, the conjugate dienes (1,3-butadiene and 1,3-hexadiene) yielded only a mixture of butenes and hexenes without any alkanes being observed. When quenched with D_2O only 41% of the product showed deuterium incorporation. The non-conjugated diene, 1,5-hexadiene, in THF yielded a mixture of 10% 1-hexene and 80% hexane with 75% deuterium incorporation when quenched with D_2O . However, in benzene only, methylcyclopentane was observed with 90% deuterium incorporation when quenched with D_2O . Evidently, in benzene cyclization takes place (eq. 3)⁴¹ whereas in THF cyclization



S = solvent

does not take place because THF is strongly coordinated to aluminum and therefore is difficult to be displaced since the electron demand of the aluminum is somewhat satisfied. In benzene, however, rearrangement is still possible.

Survey of Catalysts of Hydrometallation of Internal Alkenes

According to the literature, all attempted catalytic hydrometallation reactions involving internal olefins result in at least some isomerization to the terminally substituted products after quenching. It would be desirable to be able to hydrometallate internal alkenes without isomerization. Therefore a series of transition metal halides were allowed to react as catalysts with $\text{HAl}(\text{NPr}_2)_2$ and cis-2-hexene in benzene at 60°C for 24 hours (Table 13). After the allotted time, the reactions were quenched with a benzene solution of iodine. The products were analyzed by glc. Under these conditions no 2-iodohexane was observed al-

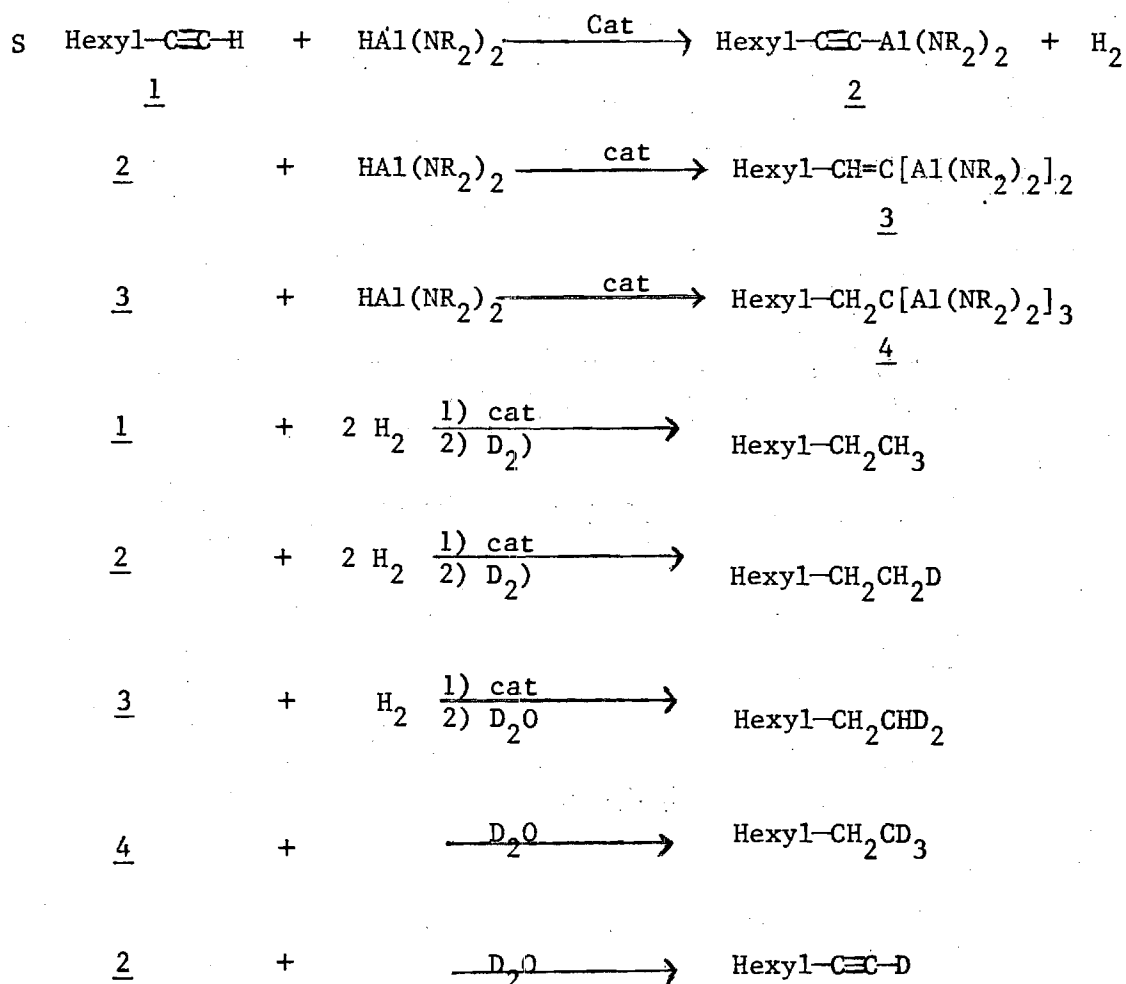
though the cobalt and nickel catalysts produced nearly quantitative yields of hexane (99%). The titanium catalysts (TiCl_3 , TiCl_4 and Cp_2TiCl_2) provided 1-iodohexane in 55, 56, and 75% yields respectively accompanied by 5-13% trans-2-hexene. When the reaction with Cp_2TiCl_2 was allowed to proceed at room temperature for 24 hours in benzene or THF, only a trace of 1-iodohexane, none of the 2-iodohexane, 85% cis-2-hexene, and 14% trans-2-hexene were detected by glc. Therefore one can conclude from these data that the catalytic hydrometallation of internal alkenes proceeds with isomerization.

Reactions of Alkynes

The results obtained from the reactions of various alkynes with $\text{HAL}(\text{NPr}^i_2)_2$ and 5 mole percent Cp_2TiCl_2 in benzene at room temperature under an argon atmosphere are tabulated in Table 14. In the case of the internal alkyne (2-hexyne, 2-octyne, 1-phenylpropyne and diphenylethyne, Table 14) reactions, a small amount (5, 10, 3 and 0% respectively) of the alkane was observed by glc. This by-product could be minimized to about 3% conducting the reaction at 0°C in an 80:20 mixture of benzene/THF for 2 hours. The major products were cis-2-hexene (94%), cis-2-octene (90%), cis-1-phenyl-1-propene (96%) and cis-stilbene (96%) with only 1-4% of the trans-isomer observed. All the products were confirmed by comparing the ir spectra of identical samples obtained by the hydrogenation of the starting materials (Pd/C and hydrogen) or samples obtained from the Aldrich Chemical Company. When the reaction mixtures were quenched with D_2O , 96-97% of the cis-alkenes (Table 14) contained deuterium according to mass spectroscopy. When the reaction with 2-hexyne was quenched with iodine, the nmr spectrum showed a 53:47 ratio of 2-iodo-cis-2-hexene to 3-iodo-

cis-2-hexene (Table 14). This result is expected on steric as well as electronic grounds since there is little difference in either effect between alkynyl methyl and propyl groups.

A study was conducted in order to determine (1) the effect of temperature on the products of reaction and (2) the product composition from 0 to 100% reaction. A representative internal alkyne, 2-hexyne, was allowed to react with $\text{HAL}(\text{NPr}_2)_2$ in the presence of various amounts of Cp_2TiCl_2 . The results are summarized in Tables 15 and 16. When the reaction was carried out at room temperature for 16 hours only 52% deuterium incorporation in the product was observed; however, when the reaction was carried out at 0°C , 91% deuterium incorporation was observed, once again indicating formation of the intermediate cis-2-hexenylaluminum compound in high yield. This reaction is believed to be reversible as shown in Scheme 6; however, this result indicates that either the alkenyltitanium or alkenylaluminum compound is not stable at room temperature under hydrometallating conditions and subsequently undergoes decomposition to produce H_2 which, in the presence of catalyst, will hydrogenate the alkyne to the alkene which in turn can be hydrogenated to the alkane. This suggestion would account for the low deuterium content of the product following work up procedures. A separate experiment showed that hydrogen was indeed produced when $\text{HAL}(\text{NPr}_2)_2$ was added to Cp_2TiCl_2 at room temperature. Hydrogen was also produced when diisobutyloctenylaluminum in benzene was added to 5 mole percent of Cp_2TiCl_2 . The diisobutyloctenylaluminum was prepared according to the procedure of Wilke which allowed 1-octyne to react with diisobutylaluminum hydride at 60°C . This result also supports the above proposition. The amount of alkane which was produced from



Scheme 8: Proposed Mechanism for the Polydeuterated Octane Formation.

catalyst had little effect on the product ratios.

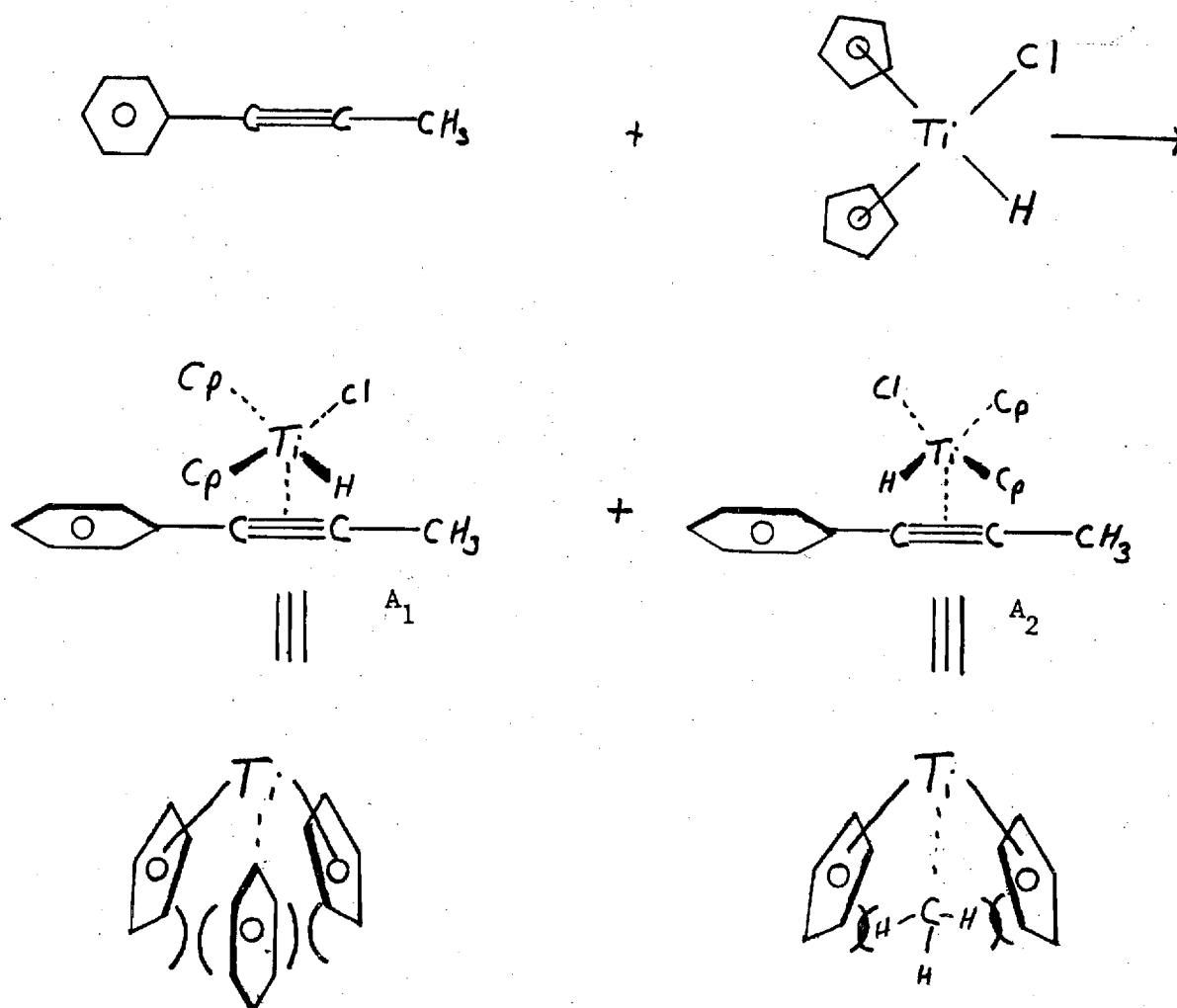
In order to circumvent the problem of producing a wide variety of products discussed above, the trimethylsilyl compound was prepared according to equation 4. When 1-trimethylsilyl-1-octyne was allowed to

the reaction of 2-hexyne with $\text{HAl}(\text{NPr}_2)_2$ in the presence of Cp_2TiCl_2 was reasonably constant throughout the reaction at 0°C indicating that the alkane is formed in the initial stages of the reaction by hydrogenation. Also considerable trans-olefin is formed when the temperature is increased from 0 to 25°C indicating the advantage of lower reaction temperatures. If the alkyne was added after the catalyst and alkane were allowed to react with stirring for a few minutes under a slight vacuum, the amount of alkane produced decreased to less than 3%, but the amount of alkene also decreased to 45% with 94% deuterium incorporation.

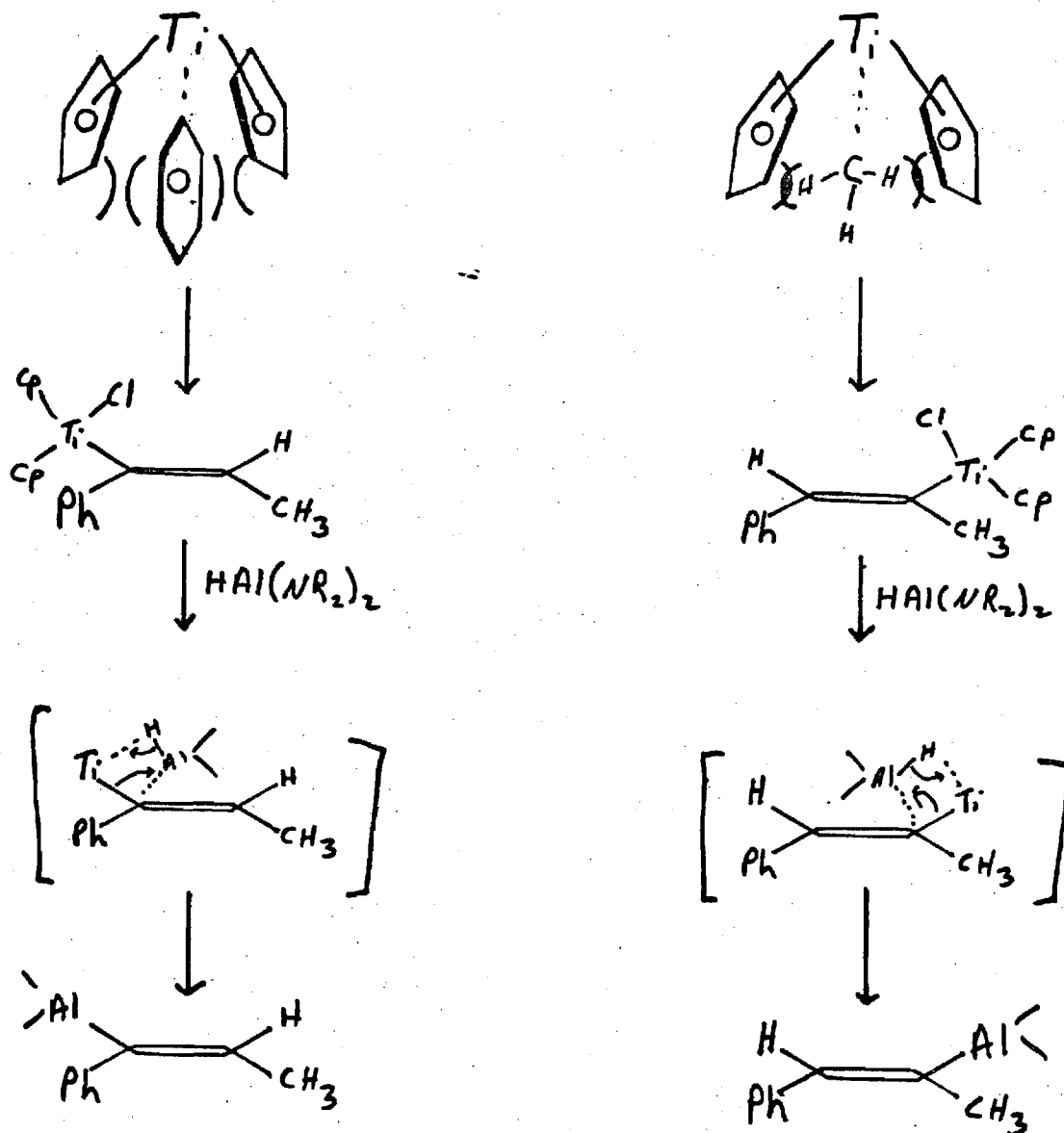
As the amount of catalyst was increased (Table 17) the rate also increased with no loss in deuterium incorporation. A reasonable catalyst concentration is considered to be 5 mole %.

If 1-phenylpropyne was allowed to react under similar conditions (Table 14), 96% of cis-1-phenyl-1-propene, 3% of phenylpropane and 1% of trans-1-phenyl-1-propene were produced upon quenching with water. The cis-alkene produced in this manner matches the nmr, ir, mass spectrum and refractive index of cis-1-phenyl-1-propene obtained from the catalytic hydrogenation of 1-phenylpropyne. When the catalytic hydrometallation reaction was quenched with D_2O , the product contained 97% deuterium according to mass spectroscopy. The nmr spectrum showed a 10:90 ratio of 2-deuterio-cis-1-phenyl-1-propene to 1-deuterio-cis-1-phenyl-1-propene (Table 14). However, Eisch⁴² reported that quenching the reaction of diisobutylaluminum hydride and 1-phenylpropyne at 50°C with D_2O produced an 80:20 ratio of the 2-deuterio-cis-1-phenyl-1-propene to 1-deuterio-cis-1-phenyl-1-propene indicating that attack occurred at the least hindered carbon 4 to 1. The reverse regiochemistry observed for the

Scheme 7: Proposed Mechanism For The Catalytic Hydrometallation Of 1-Phenylpropyne.

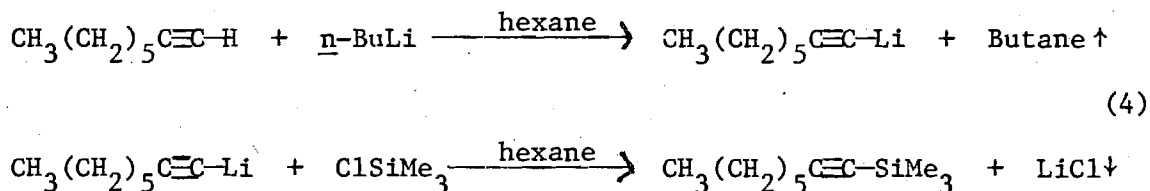


Scheme 7 (Continued)



hydrometallation reaction products reported herein indicates, according to Scheme 7, that the formation of the titanocene hydridochloride-alkyne complex determines the regiochemistry of the products. Complex A_1 is less hindered than complex A_2 , because the cyclopentadienyl and phenyl groups in complex A_1 can adapt a staggered arrangement, but the cyclopentadienyl and methyl groups in complex A_2 cannot. Therefore complex A_1 would be favored over complex A_2 . Of course, the titanium hydridochloride catalyst could also be complexed to the π cloud of the phenyl ring thus positioning the titanium closer to the carbon holding the phenyl ring. Following the β -hydride addition, the transmetallation step with $HA1(NPr^i_2)_2$ would generally have the same environment and therefore would have little effect on the overall reaction products.

When a representative terminal alkyne (e.g. 1-octyne) was allowed to react under the above conditions, an approximately 50:50 mixture of alkane to alkene was observed. When the reaction mixture was quenched with D_2O , the alkene showed a relatively high percentage of deuterium incorporation (78%); however, the octane showed deuterium only to the extent of 55%. According to mass spectroscopy, four octanes [octane- d_0 (45%), octane- d_1 (22%), octane- d_2 (18%) and octane- d_3 (15%)] were produced which Scheme 8 can account for.⁴² The deuterium incorporation exhibited in the octane products indicates that metallation or deprotonation of the acetylenic hydrogen occurs with subsequent addition of H-Al across the multiple bond.⁴² Also, with hydrogen present along with a catalyst, hydrogenation reactions are possible and thereby accounting for the large number of products. The lowering or raising the temperature, increasing the reagent/alkyne ratio or increasing the amount of



react under the usual catalytic hydrometallation conditions (Table 14), only 5 percent of the totally saturated compound, octane-d₀, and the trans-alkene were produced with the cis-alkene being the predominant product (90%). This product's nmr, ir and mass spectra matched those obtained for the product from the hydrogenation of 1-trimethylsilyl-1-octyne by Pd/C and hydrogen. When the hydrometallation reaction product was quenched with D₂O, 80% of the product contained deuterium according to mass spectroscopy. NMR analysis of the products showed that approximately 90% (Table 14) of the deuteriated compound was the cis-1-trimethylsilyl-2-deutereo-1-octene. This result is somewhat surprising in that one would expect the aluminum to be adjacent to the more electro-negative silicon atom.⁴² However, as shown earlier in Scheme 7, the regiochemistry of the product is determined by formation of the intermediate alkynyl titanium compound. The bulky trimethylsilyl group hinders the approach of the titanium catalyst and therefore 90% of the newly formed titanium compound is located in the 2-position. An indication of this is that a similar result was obtained when HAl(NEt₂)₂ was used as the reagent.

Further Reactions With Carbonyl Compounds and Oxygen

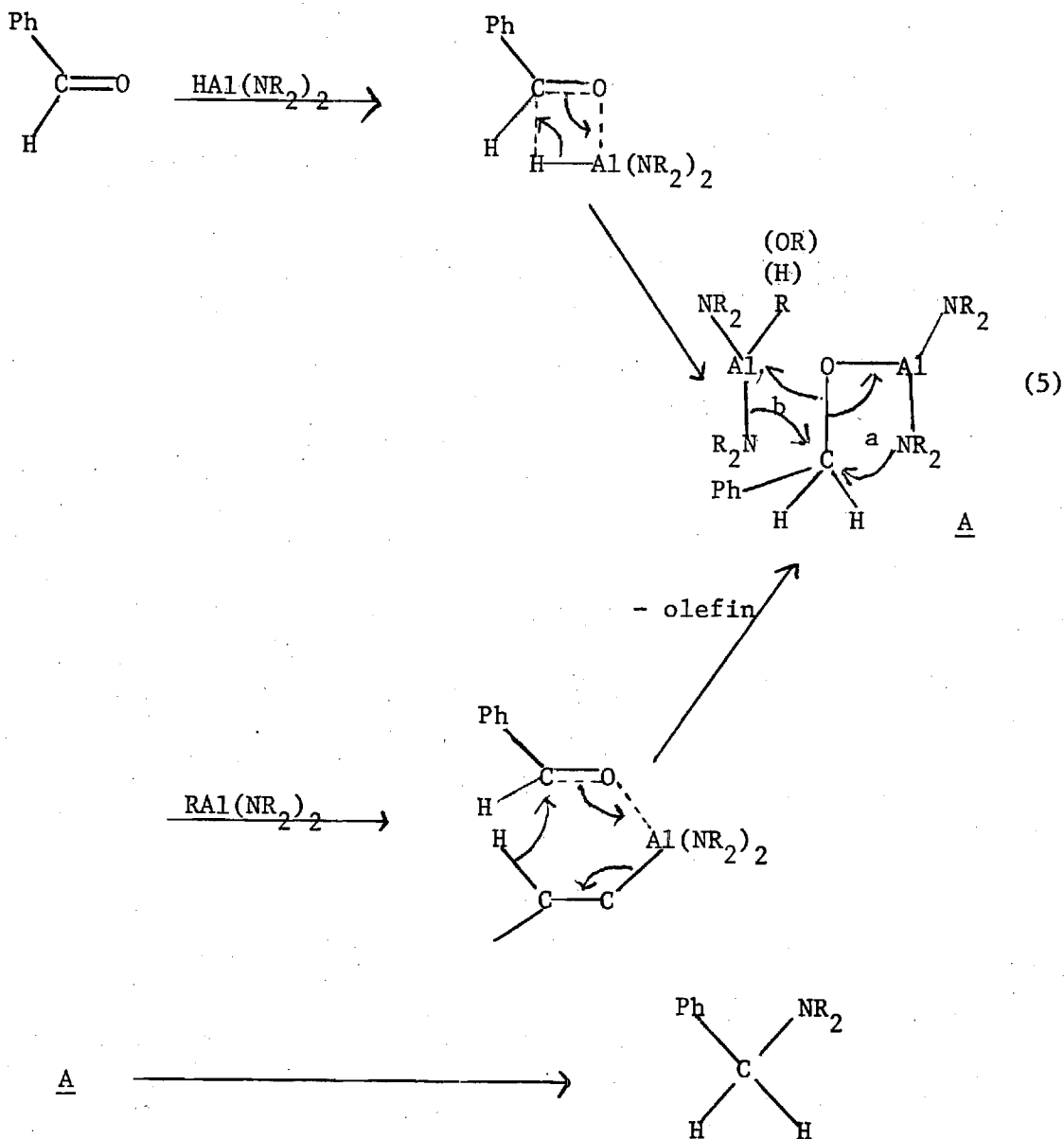
In order to evaluate the extent to which further reactions (other than reactions with D_2O or halogens) can be applied to the newly formed hydroaluminated species, stoichiometric amounts of acetone, benzaldehyde and benzophenone were added to the reaction mixtures and allowed to react at room temperature and at $30^\circ C$ for an additional 24 hours. The results are listed in Table 18. First, $HA1(NPr_2^i)_2$ was allowed to react with acetone, benzaldehyde, 4-t-butylcyclohexanone and benzophenone in a 2:1 ratio in benzene. The alane reduced the non-enolizable carbonyl compounds, benzaldehyde and benzophenone, in 100% yield to the corresponding alcohols. However, acetone was reduced to yield 40% of isopropanol with 35% of the starting ketone recovered and the remaining ketone presumably lost through condensation resulting from enolization. This alane also reduced 4-t-butylcyclohexanone to provide 18% axial alcohol and 82% equatorial alcohol in a 45% overall yield with 30% recovered ketone. The relative ratio of alcohols is approximately the same as AlH_3^{43} in THF (19% axial alcohol). However, in benzene, $HA1(NPr_2^i)_2$ in a 2:1 ratio of reagent to ketone provided 30% of the axial alcohol and 70% of the equatorial alcohol in a 45% yield with 30% of the ketone recovered. To a lesser degree, this result is reminiscent of the trialkylaluminum reactions in benzene compared to those in THF.

When 1-octene was added to $HA1(NPr_2^i)_2$ and allowed to react under hydrometallation conditions and then the reaction mixture added to acetone or vice versa, there was produced only 5% isopropanol, 2% of the addition product (2-methyl-2-decanol), and 70% acetone. The analogous reaction with 4-octyne produced essentially the same results. When

benzaldehyde was allowed to react with the hydrometallated species formed from the reaction of 1-octene or 4-octyne with $\text{HAL}(\text{NPr}_2)_2$ and Cp_2TiCl_2 , the major product was benzyldiisopropylamine (90%). When $\text{HAL}(\text{NEt}_2)_2$ was used as the hydrometallating agent, 90% of benzyldiethylamine was produced. When benzophenone was allowed to react with $\text{HAL}(\text{NEt}_2)_2$ or $\text{HAL}(\text{NPr}_2)_2$, 62% of the corresponding amine (Ph_2CHNR_2) was produced in addition to 38% benzhydrol. Only a trace of the expected addition product was observed. All products were determined by methods discussed in the experimental section.

These latter developments were only recently observed in this study. Therefore more experiments must be carried out in order to determine the extent to which this reaction can be of synthetic utility. Stoichiometry, solvent, temperature and rate studies must be carried out in order to maximize the production of the amine. Also, other enolizable and non-enolizable carbonyl compounds should be allowed to react under these conditions along with the necessary control experiments. That is, independently prepared alkyl and alkenyl bis-dialkylaminoaluminum compounds should be allowed to react under these conditions with and without the presence of catalyst. If a catalyst is necessary then a survey of catalysts should be carried out.

It is proposed that β -reduction by the newly formed $\text{RAL}(\text{NR}_2)_2$ compound or direct reduction by $\text{HAL}(\text{NR}_2)_2$ of the carbonyl group takes place first forming an alcoholate which can then be displaced intramolecularly (a) or intermolecularly (b) (eq. 5). If this is the case,



then alcohols should be allowed to react under these conditions which would indicate if the alcoholate is indeed the intermediate. If alcohols can produce tertiary amines under these mild conditions, it would represent a major development since there are very few methods to prepare amines from alcohols in one step without the use of exotic reagents and/or drastic conditions.⁴⁵

It is known that R_3Al compounds undergo rapid oxidation with O_2 to produce, on hydrolysis, alcohols¹⁹ or with CO_2 to produce tertiary alcohols or carboxylic acids depending on the reaction conditions.⁴⁶ When oxygen or carbon dioxide was passed through the catalytic hydro-metallation reaction mixture of 1-octene and $HAL(NR_2)_2$ in the presence of Cp_2TiCl_2 , only octane was observed by glc after work up with saturated ammonium chloride or 10% HCl. The reason for this may be argued on inductive electron withdrawing grounds. On the electronegativity scale,⁴⁷ carbon has a value of 2.5 while the value of nitrogen is 3.0. This means that nitrogen withdraws electron density from the adjacent carbon atom thereby strengthening the aluminum-carbon bond compared to R_3Al compounds (Figure 2). The electron donating ability of the NR_2 group by resonance

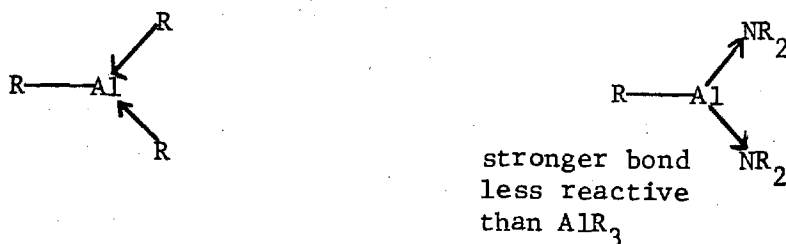


Figure 2

is diminished because the orbital size difference between aluminum and nitrogen prohibit good overlap thus the overall effect is inductive explaining the lack of reaction of $Al(NR_2)_2$ with CO_2 or O_2 . Credence is given this supposition by the fact that when triethylaluminum in benzene was oxidized in the presence of 5 mole percent of Cp_2TiCl_2 , n-propanol was prepared.

Survey of Substituted Alanes

As stated above, bis-dialkylaminoalanes in the presence of 5 mole percent Cp_2TiCl_2 proved to be an excellent reagent for accomplishing catalytic hydrometallation. However, in order to study the scope of reagents successful in this reaction, it was decided to investigate the effects of other substituted alanes on the catalytic hydroalumination of a representative olefin (e.g. 1-octene). Table 18 lists the results of this investigation. As discussed above the bis-diisopropyl- and bis-diethylaminoalanes produced high yields of 1-iodooctane (80 and 86%, respectively) and octane- d_1 (93 and 90%, respectively) when quenched with the appropriate reagent. The mono- and dichloroalanes under catalytic hydroalumination conditions produced 97% octane with 85% and 83% deuterium incorporation, respectively. Sato, et al.,¹⁹ reported a 90% yield of hexane when AlH_2Cl or AlHCl_2 was allowed to react with 1-hexene in the presence of 2% TiCl_4 at 15°C for 6 or 16 hours, respectively. Unfortunately, these reactions were not quenched with D_2O , halogen, etc. processes which would indicate the extent to which the hydroaluminated species was formed. The decrease in rate for HAlCl_2 compared to H_2AlCl observed by Sato, et al.,^{19c} was also observed in the present work. We found that 2-5% of Cp_2TiCl_2 increased the rate of reaction compared to that observed by Sato,^{19b,c} but a relative rate decrease was also observed going from H_2AlCl to HAlCl_2 , 2 and 6 hours, respectively. The relative decrease in reaction rate maybe due to the electron withdrawing ability of the chlorine atom which results in the strengthening of the Al-H bond (Figure 3) thus making it less reactive than AlH_3 towards Cp_2TiCl_2 as well as the

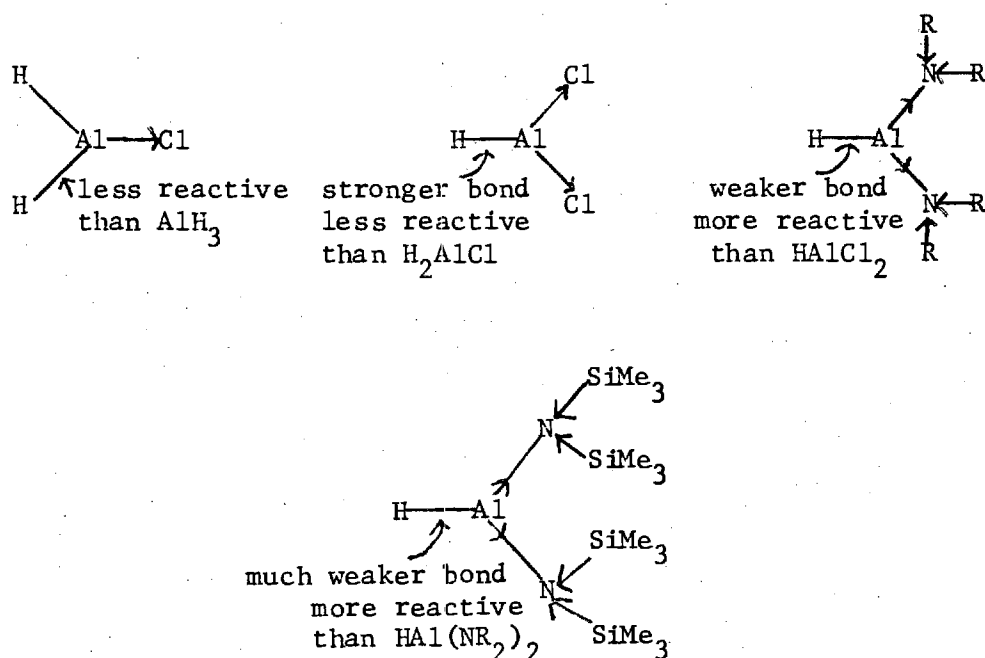
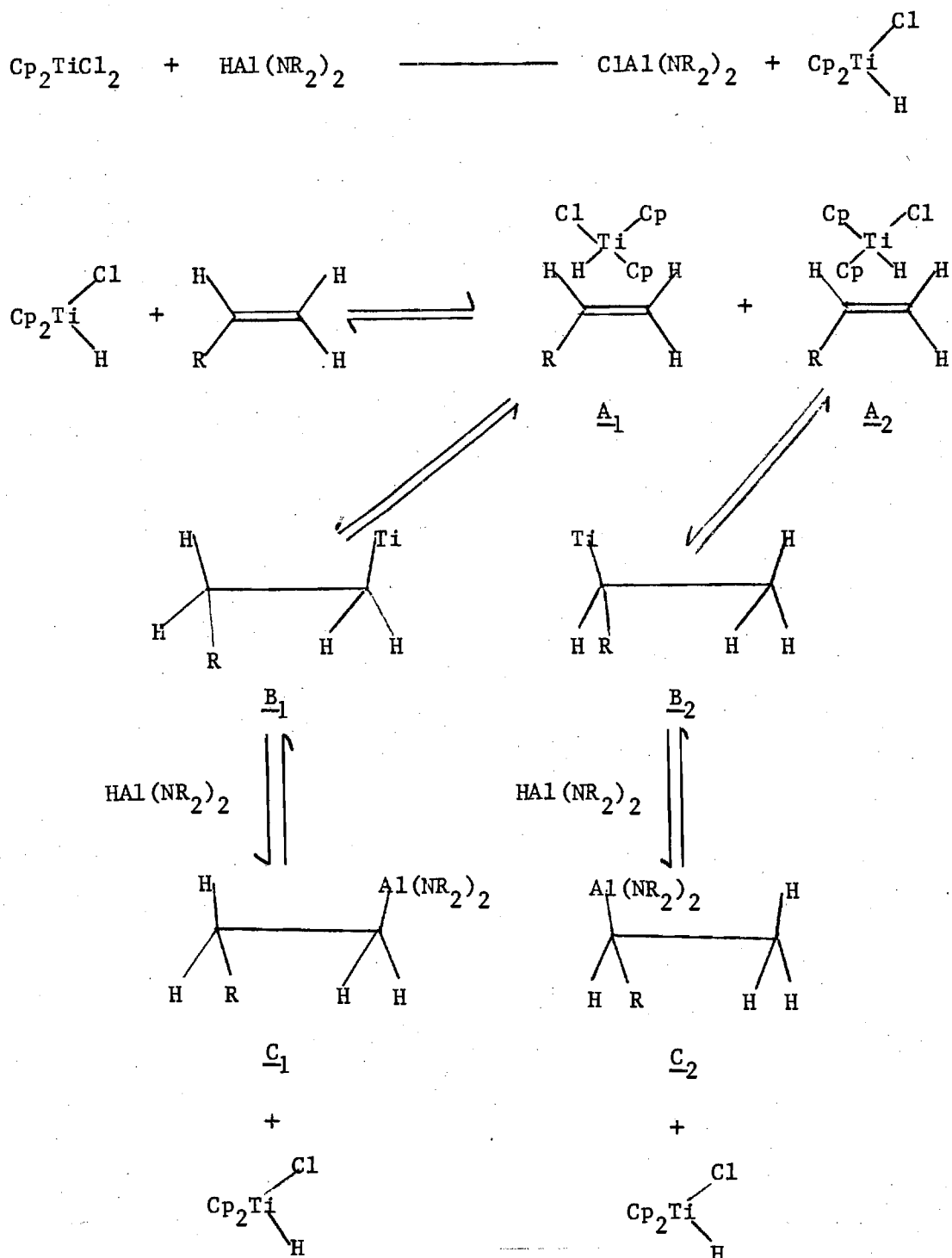


Figure 3

transmetallation step described in Scheme 6. When two chlorine atoms are present, the effect is even greater resulting in even a slower rate. This effect is even noticeable when comparing $\text{Al}(\text{NR}_2)_2$ compounds with AlCl_2 . The electronegativities of nitrogen and chlorine are equal (3.0⁴⁷); however, because alkyl groups are attached to the nitrogen atom, the effect is diminished somewhat by inductive electron donation, and therefore the H-Al bond is weaker and accordingly, more reactive, and thus these reactions are complete in approximately 15 minutes. In the case of bis-1,1,1,3,3,3-hexamethyldisilazoalane, this effect is also observed. When this reaction was quenched with iodine, both the 1- and 2-iodooctane were produced in a relative ratio of 53:47 with a 90% yield, whereas, when all of the other reactions were quenched with a benzene solution of iodine, only the 1-iodooctane was obtained. This latter result maybe explained

in the following manner. On the electronegative scale aluminum, silicon and nitrogen have values of 1.5, 1.8 and 3.0, respectively.⁴⁷ Silicon is a very good electron donor and the nitrogen is a good electron acceptor. Therefore, the amount of electron density on the aluminum is not decreased as much as in the other cases discussed above. This results in a more reactive H-Al bond. In Scheme 9, we proposed that there exists an equilibrium between the two complexes of the titanium hydride and the olefin (A_1 and A_2). If the formation of the titanium hydride or the transmetallation step depends on the reactivity of the alane, then it can be seen that the more reactive the alane the greater the possibility of forming compound B_2 which would eventually lead to the formation of 2-iodooctane. This, evidently, was the case with the disilazane derivative reaction which was over in about 10 minutes at room temperature. Once compounds B_1 and B_2 are formed, both are likely to undergo a transmetalation reaction with $HAL(NR_2)_2$ to form C_1 and C_2 . These products in turn can produce the 1- and 2-deuterio of iodoalkenes when quenched with D_2O or iodine.

When a more electronegative atom such as oxygen (electronegative value of 3.5⁴⁷) is incorporated into the reagent, the reaction is slowed down even more because of a stronger and less reactive H-Al bond which was demonstrated for the H_2AlOMe , $HAL(OMe)_2$, $HAL(OPr^i)_2$ and $HAL(OBu^t)_2$ reagents. For the alkoxy derivatives which were insoluble in THF or benzene only the monomethoxy reagent produced 10% octane after 24 hours at room temperature and quenched with water. The diisopropoxy and di-t-butoxy derivatives which were more soluble in THF produced only a 15% yield of octane.



Scheme 9: Proposed Mechanism for the Production of the Kinetic and Thermodynamic Products from the Catalytic Hydrometallation Reaction

Hydrometallation With LiH

Recently Caubere and co-workers showed that NaH-RONa-MX_n systems were capable of reducing halides,^{48,49} ketones, alkenes and alkynes.^{50,51} However, these reactions were not catalytic, but did provide 75-95% of the corresponding alkanes, alcohols, alkanes and alkenes respectively. In our continuing studies of catalytic hydrometallation reactions, we investigated the reactions of activated LiH with alkyl halides, carbonyl compounds, alkenes and alkynes in the presence of catalysts. Table 19 lists the results of the reaction of activated LiH and transition metal halides with 4-t-butylcyclohexanone in 1:1:1 ratio. Without the transition metal halide only a 5% yield of the alcohols were obtained with 55% being the equatorial alcohol. However, an equal molar ratio of VCl_3 with respect to LiH provided an 86% yield of the alcohols with 82% being the axial isomer, FeCl_3 reduced 68% of the ketone providing 74% of the axial alcohol. A catalytic amount of VCl_3 (5 mole percent) was added but under these conditions only 3% of the alcohols were obtained with basically the same stereoselectivity observed for the stoichiometric reaction.

Table 20 represents the reactions of LiH-VCl_3 in 1:1 ratio with other carbonyl substrates. The ketones (4-t-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, 2-methylcyclohexanone and camphor) were reduced in high yields with the axial or exo alcohols predominant (78, 90, 92 and 95% respectively). The aldehydes (hexanal and benzaldehyde) and esters (ethyl benzoate and ethyl n-butyrate) were also reduced to their respective alcohols (95, 97, 93 and 95%) in high yields. In the case of ester reductions, small amounts of the corresponding aldehydes were also observed.

When alkenes were allowed to react under similar conditions, only

the terminal alkenes (1-octene, 2-ethyl-1-hexene and methylene cyclohexane) reacted to form the corresponding alkanes in high yield (Table 21). However, none of the reactions produces high percentages (29 and 30%) of deuterium incorporation when quenched with D_2O . Changing solvents from THF to benzene had no effect on the outcome.

In an attempt to improve on the work reported by Caubere, we decided to explore, in a cursory sense, the possibility of catalytic (5 mole %) hydrometallation using LiH or NaH. Table 22 summarizes the results of this study. Of all the transition metal halides surveyed, Cp_2TiCl_2 produced the most encouraging results when allowed to react with activated LiH and a representative olefin, 1-octene. A 77% yield of octane was produced, and if the reaction was quenched with D_2O , 50% deuterium incorporation was observed by mass spectroscopy. It was somewhat disappointing that NaH did not produce yields larger than 5% of octane, because from an economic point of view, NaH is inexpensive and easy to handle.

If alkynes (Table 23) or enones (Table 24) were allowed to react with $LiH-VCl_3$ in 1:3 ratio, only starting material was recovered in all cases after 36 hours at $45^\circ C$ (except for the reaction of cinnaldehyde which produced 90% of the 1,2 reduction product). Evidently the other enones either enolized or were too bulky for reaction to take place.

Hydrometallation Reactions With Main Group Complex Metal Hydrides

Sato, et al.¹⁹ reported that titanium tetrachloride and zirconium tetrachloride catalyzed the addition of lithium aluminum hydride to olefinic double bonds to produce the organoaluminate. They reported, for example, that 1-hexene produced 99% n-hexane when allowed to react in

THF at room temperature for 30 minutes in the presence of 2 mole % of TiCl_4 . However, the reactions were not quenched with D_2O a process which would monitor the production of the hydrometallated intermediate. When these reactions were quenched with bromine, only 70% of the corresponding bromide was obtained in most cases. Therefore the product obtained from the quenching of the reaction with H_2O was misleading.

In order to clear up this question, we investigated the above reaction in more detail. Lithium aluminum hydride, sodium aluminum hydride, lithium trimethylaluminum hydride, sodium trimethylaluminum hydride, lithium and sodium bis-dialkylaminoaluminum hydride and Vitride (sodium bis(2-methoxyethoxy)aluminum hydride) were allowed to react with a series of alkenes and alkynes in a ratio of alkene or alkyne to reagent of 2:1 in the presence of 2 mole % Cp_2TiCl_2 . The results are listed in Table 25. The catalyst used in this study was titanocene dichloride, Cp_2TiCl_2 , because it worked so well in the previously studied hydrometallation reaction with bis-dialkylaminoalanes. All of the hydrides provided similar results. When allowed to react with terminal alkenes, the reactions were over in 10 minutes at room temperature. After quenching with D_2O , the products were analyzed via mass spectrometry. The mass spectrum of the products were compared to the mass spectrum of the deuterated species obtained from quenching the corresponding Grignard Reagents with D_2O . The % deuterium incorporation in the product was considered an indication of the intermediate formation of hydrometallated species. All terminal alkenes (1-octene, 1-hexene, styrene, methylenecyclohexane, 2-ethyl-1-hexene and neohexene) provided high yields of deuterium incorporation (95-100%) except for the neohexene reaction which

only showed 55% deuterium incorporation. As for the bis-dialkylamino-alumination reaction discussed above, steric reasons are probably responsible for this result. Another observation in this study which parallel the bis-dialkylaminoalumination reaction is that the overall yield of the alkane decreased in the following manner: octane (98%) ~ hexane (99%) > ethylbenzene (85%) > methylcyclohexane (70%) ~ 2-ethylhexane (70%) > neohexane (60%).

The internal alkenes (cis-2-octene, cis-2-hexene and trans-2-hexene) once again showed great difficulty in becoming hydrometallated. In all cases only low yields (1-5%) of alkanes were observed. The reactions were carried out as described above with the reaction time increases to 36 hours. The reaction temperature was also increased to 60°C but only small amounts of alkanes were observed (1-5%). Sato¹⁹ found that the internal alkenes could be hydroaluminated if the reactions were carried out for 120 hours at 60°C and in the presence of TiCl_4 or ZrCl_4 . We were hoping that Cp_2TiCl_2 would provide milder conditions, but unfortunately this did not happen.

For terminal alkynes, (1-octyne and phenylethyne) the same problems associated with the bis-dialkylaminoalumination reactions namely the deprotonation of the acetylenic proton, and further addition were very prevalent in these reactions (See Scheme 7). Only small amounts of alkenes (3-10%) and alkanes (4-13%) were observed. The starting alkyne showed a great amount (85%) of deuterium incorporation when the reaction was quenched with D_2O . By lowering or raising the temperature, no major effect was observed except that the rate was affected in the expected way. Normally, all reactions were conducted at room temperature for 2 hours in

a reagent to alkyne ratio of 1:2 in the presence of 2 mole % of Cp_2TiCl_2 . By lowering the temperature to 0°C , after 2 hours, only a trace of alkene or alkane was observed. After 12 hours, 10% (the same amount observed at room temperature) alkene and alkane were observed. Longer reaction times showed no improvement. By raising the temperature to 50°C , the amount of alkane increased to 30% after 30 minutes. After 2 hours 40% octane and 45% octene were observed. If the reaction was quenched with D_2O , the product incorporated only 50% deuterium. It was noticed by earlier workers in this group that 1-octyne and phenylethyne could be reduced to 1-octene (99%) and styrene (94%) in high yields by LiAlH_4 ⁵² with catalytic amounts of NiCl_2 . Unfortunately deuterium analysis was not conducted. Therefore the author repeated this experiment and quenched it with D_2O after 48 hours at room temperature in THF. The amount of deuterium incorporation was only 15%.

The internal alkynes (4-octyne, 2-hexyne, phenylpropyne and 1-trimethylsilyl-1-octyne) were allowed to react under the conditions described above. 4-Octyne and 2-hexyne produced 99% and 100% cis-4-octene and cis-2-hexene respectively with 100% deuterium incorporation for both. The nmr spectrum of the product from 2-hexyne showed a 53:47 ratio of 2-deuterio- to 3-deuterio-cis-2-hexene. When this reaction was quenched with a benzene solution of iodine, 95% of the corresponding vinyl iodo-compounds were obtained. For the 2-hexyne reaction, a 51:49 ratio of 2-iodo- to 3-iodo-cis-2-hexene was obtained. For the phenylpropyne case, 15% 1-phenylpropane, 70% of cis-1-phenyl-1-propene and 15% 3-phenyl-1-propene were obtained under these same conditions. The 3-phenyl-1-propene contained 85% deuterium and the phenylpropane contained only 55% deuterium. These

results indicate potential for the production of vinylaluminates which have been shown to undergo further reaction with CO_2 , cyanogen and halogens to form α, β -unsaturated nitriles and vinyl halides.⁵²

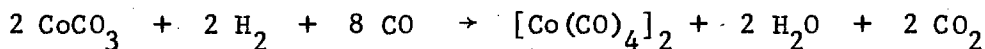
As noted earlier, the terminal octyne reactions were not clean. Therefore, 1-trimethylsilyl-1-octyne was prepared by the reaction of 1-octynyllithium with chlorotrimethylsilane as described earlier. When this alkyne was allowed to react under similar conditions, the reaction was slow even at 60°C . The best results were a 35% yield of cis-1-trimethylsilyl-1-octene (65% deuterium incorporation) and a 15% yield of 1-trimethylsilylhexane (20% deuterium incorporation).

In conclusion, these hydroalumination reactions work very well for terminal alkene and internal alkynes but not for internal alkenes and terminal alkynes. An interesting observation which is a result of this work is that the regiochemistry involved for both the bis-dialkylamino-alane and aluminate reactions is approximately the same. This indicates that the regiospecific step must be the same for both reactions. Therefore it is logical to suggest that the complexation of the intermediate titanium hydrido compound or formation of the alkyltitanium compound is the rate determining step after which the subsequent steps of Schemes 1, 2 and 3 follow.

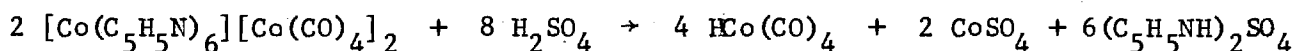
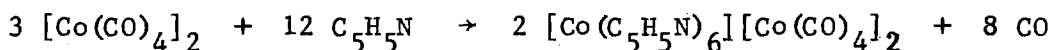
Reductions Using $\text{HCo}(\text{CO})_4$

Because of the nature of our research, we thought it would be appropriate to continue our search for stereoselective reducing agents by investigating the reduction of ketones, aldehydes, enones and alkyl halides by transition metal hydrides such as $\text{HCo}(\text{CO})_4$ (easily prepared from dicobalt octacarbonyl). Dicobalt octacarbonyl $[\text{Co}(\text{CO})_4]_2$, was

prepared according to a procedure by Orchin.⁵³ Cobalt carbonate was



heated to 160°C (with hydrogen and carbon monoxide in an autoclave pressurized to 3,500 psi) for 3 hours. Dicobalt octacarbonyl prepared in this manner was first allowed to react with distilled pyridine to form the pyridine adduct which after further reaction with concentrated sulfuric acid produced cobalt hydrocarbonyl, $\text{HCo}(\text{CO})_4$. The hydride formed



at 0°C and was distilled quickly by bubbling CO through the solution and trapped in a liquid nitrogen trap; however, carbon monoxide also condensed under these conditions. The CO was then allowed to evaporate slowly leaving behind the $\text{HCo}(\text{CO})_4$ which was dissolved in hexane and stored at -78°C.

Hydrogenations of organic compounds are very well documented under "oxo process" conditions.^{54,55} Goetz and Orchin⁵⁶ have reported that when α, β -unsaturated aldehydes and ketones are treated with $\text{HCo}(\text{CO})_4$ under "oxo" conditions, the olefinic linkage is reduced rather than hydroformylated. They also showed that $\text{HCo}(\text{CO})_4$ in hexane reacted with saturated aldehydes at room temperature to give the corresponding alcohols at a rate much slower than the reactions with olefins under the same

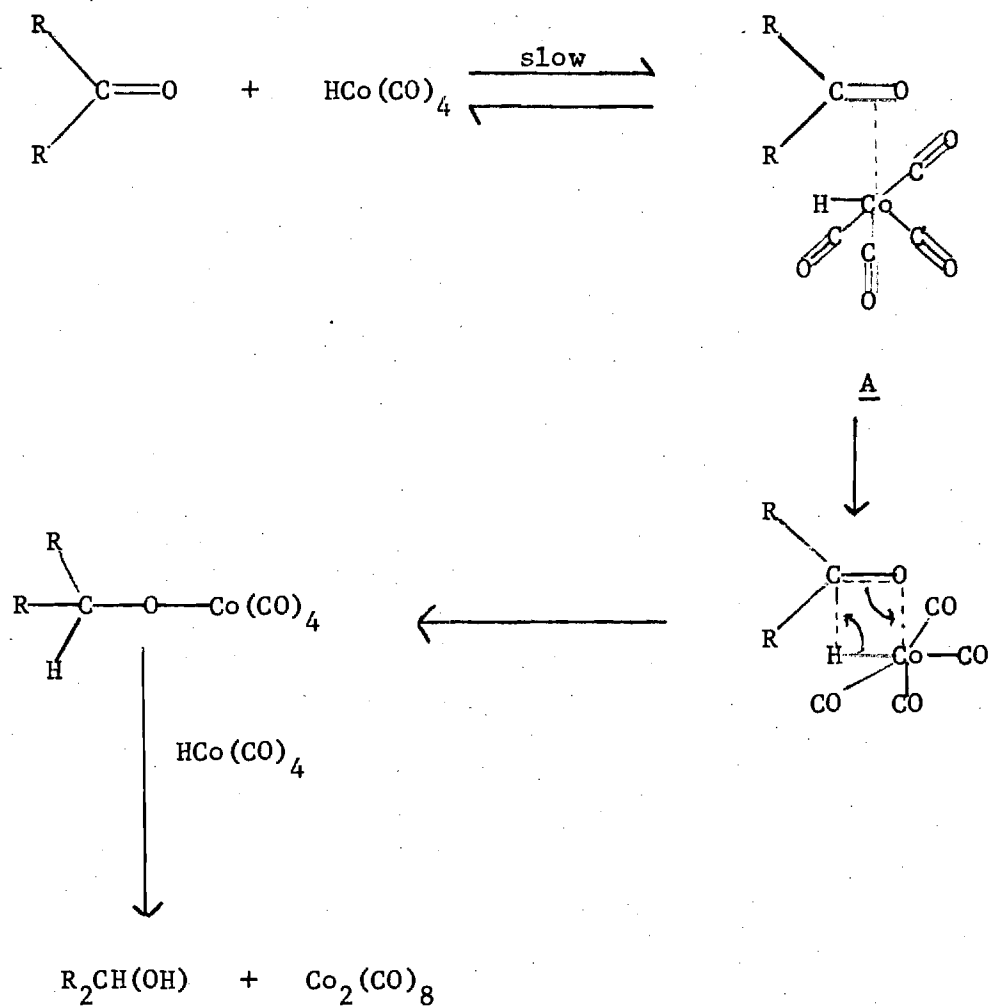
conditions. Thus it might be suspected that the reduction of saturated ketones would also be slow. However, we wanted to observe the stereoselectivity of HCo(CO)_4 towards 4-t-butylcyclohexanone and 2-methylcyclohexanone under various conditions (Table 26). We found that the reduction at -20°C , 0°C , RT and 45°C for 12 hours produced only 0-5% of the corresponding alcohols with an axial to equatorial ratio of 53:47 and 60:40, respectively. When the reactions were carried out at 45°C , decomposition of HCo(CO)_4 became very rapid. At the other temperatures, the reduction of the ketones took place very slowly. It was anticipated that this reduction would be stereoselective; however, this was not the case.

Evidently, the reaction goes through a pathway suggested by Orchin and Goetz⁵⁶ for aldehydes and α,β -unsaturated aldehydes and ketones (Scheme 10). A semiquantitative kinetic study of these reagents in which the hydrocarbonyl disappearance was measured by a simple titration technique discussed in the Analytical Section indicates that the reactions are first order with respect to hydrocarbonyl. The hydrocarbonyl appears to function as a hydride donor.

The electron-releasing properties of alkyl groups should help to stabilize the complex A (Scheme 10) since cobalt is electron withdrawing. Therefore as the stability of the complex increases the reactivity of the subsequent reducing step decreases and thereby lowering the yield of alcohol as was observed.

Simple and Complex Metal Hydride Carbonylations

There is currently intense interest in catalytic reactions of carbon monoxide and hydrogen. Mechanistic considerations suggest that formation of the first C-H bond may be the key step. Casey and Neumann⁵⁷



Scheme 10: Proposed Mechanism for the Reduction of Ketones with HCo(CO)_4 .

have suggested that insertion of CO into a metal hydrogen bond is not a feasible transformation. An alternative would be nucleophilic attack by a hydride on a coordinated carbonyl. Such reactions lead to formyl,⁵⁸ hydroxymethyl⁵⁹ and methyl^{60,61} complexes using boron hydride reagents. A catalytic process involving such a step would require a transition metal hydride capable of exhibiting hydridic character, which has been observed only for several complexes of titanium⁶² and zirconium.⁶³ Examples of the reduction of CO to methane⁶⁴ or to alcohols^{65,66} have recently been reported.

Bercaw, et. al.⁶⁵ used metal clusters, $\text{Os}_3(\text{CO})_{12}$ and $\text{Ir}_4(\text{CO})_{12}$ to catalyze the reduction of carbon monoxide to methane at 140°C and ~ 2 atmospheres. They also observed stoichiometric H_2 reduction of CO to methoxide under mild conditions with $(\eta^5\text{-C}_5\text{Me}_5)_2\text{Zr}(\text{CO})_2$. The intermediate compound was determined to be $(\eta^5\text{-C}_5\text{Me}_5)_2\text{Zr}(\text{H})(\text{OCH}_3)$ which when hydrolyzed with aqueous HCl leads to $(\eta^5\text{-C}_5\text{Me}_5)_2\text{ZrCl}_2$, H_2 and CH_3OH .

Huffman, et al.⁶⁴ reported a homogeneous hydrogenation of carbon monoxide to methane using $\text{Cp}_2\text{Ti}(\text{CO})_2$. When the titanium carbonyl complex was treated with a mixture of hydrogen and carbon monoxide (3:1 mole ratio, 1 atm at 25°C) at 150°C , methane was produced. However, the reaction was not catalytic in titanium.

Schwartz and Shoer⁶⁶ reported that $i\text{-Bu}_2\text{AlH}$ (DIBAH) in the presence of Cp_2ZrCl_2 as a catalyst will reduce CO at room temperature and 1-4 atm to give, on hydrolysis, a mixture of linear aliphatic alcohols (equation 6). The DIBAH rapidly forms a complex A with Cp_2ZrCl_2 which

Rathke and Feder⁶⁷ have also reported the production of alcohols (methanol, ethanol and propanol) and formates (methyl and ethyl) using CO and hydrogen in the presence of cobalt octacarbonyl in p-dioxane at 182°C and 300 atm presumably due to the production of HCo(CO)_4 which can react with CO and incipient radicals.

Based on this background and our work, we thought that it would be possible to accomplish the above results using CO and simple or complex metal hydrides (a source of hydrogen, H_2) in the presence of a transition metal halide catalyst such as Cp_2TiCl_2 .

When we first started this work, we allowed lithium aluminum hydride, sodium aluminum hydride, alane, sodium hydride and activated lithium hydride in the presence of 10 mole percent of various transition metal halides (Cp_2TiCl_2 , TiCl_4 , NiCl_2 , CoCl_2 and FeCl_3) in THF or benzene to react under 4000 psi of 99.5% carbon monoxide obtained from Matheson Gas Products (Table 27). The only product observed was methyl formate. However, upon further investigation it was discovered that methyl formate was present in the carbon monoxide cylinder. It may be safe to assume that the methyl formate was formed inside the iron cylinder under pressure because the methyl formate was not listed as an impurity by the company. This reasoning raises the hope that methyl formate can be prepared from CO in the presence of a catalyst and hydrogen.

According to the literature, numerous reports⁶⁸ describe the preparation of methyl formate from CO and H_2 with metal catalysts and/or base in small to modest yields. However, we have as yet not been able to accomplish this transformation. During our investigation we were also hoping to observe methanol, ethanol, propanol, ethyl formate, formic acid

or acetone which have all been reported in the literature as minor products, but these have also escaped our detection (Table 27). Another possible product would be methane, but we were not set up to detect it as a reaction product and therefore are not sure whether or not it was formed in the above reactions.

CHAPTER IV

CONCLUSION

During our investigation, we discovered that terminal alkenes and internal alkynes are reduced rapidly and in quantitative yields by $\text{HAL}(\text{NR}_2)_2$, LiAlH_4 , NaAlH_4 , LiAlMe_3H , NaAlMe_3H , $\text{LiAlH}_2(\text{NR}_2)_2$, $\text{NaAlH}_2(\text{NR}_2)_2$ and Vitride, $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ in the presence of a catalytic amount of Cp_2TiCl_2 . When these reactions were quenched with D_2O or I_2 , excellent yields of the corresponding deuterium or iodo compounds were obtained in most cases. However, when benzaldehyde or benzophenone were allowed to react with bis-dialkylaminoalanes, the corresponding tertiary amines were obtained in excellent yields. This result may also indicate that alcohols may be converted to tertiary amines; however, this possibility was not tested.

Internal alkenes and terminal alkynes did not react rapidly or regioselectively when mixed with Al-H compounds in the presence of Cp_2TiCl_2 . However, for the terminal alkynes this situation was remedied by preparing the corresponding 1-trimethylsilyl derivative which reacted under hydrometallation conditions to provide the hydrometallated species in good yield. The trimethylsilyl group could then be removed by acid. Unfortunately, longer reaction times and higher temperatures were needed.

The reactions of carbonyl compounds, alkenes, alkynes and enones with activated LiH in the presence of transition metal halides were also

investigated. However, reduction of the starting materials was accomplished only when stoichiometric amounts of VCl_3 were added to the reaction mixture. Reduction of a representative carbonyl compound, 4-t-butylcyclohexanone, produced 82% of the axial alcohol in 86% yield. Aldehydes were reduced to their respective alcohols in high yields (95-97%). Esters were reduced to the alcohols in high yields (93-95%) with small amounts (5-7%) of the aldehydes produced as well. Alkynes did not react. The only α,β -unsaturated carbonyl compound to react was cinnaldehyde which produced 90% of the 1,2 reduced product only. Only the terminal olefins reacted under these conditions. 1-Octene was reduced in 77% yield with LiH in the presence of Cp_2TiCl_2 .

When simple and complex metal hydrides were allowed to react with CO under high pressure in the presence of Cp_2TiCl_2 , TiCl_4 , NiCl_2 , CoCl_2 or FeCl_3 , no products other than starting material were detected.

The reduction of ketones by $\text{HCo}(\text{CO})_4$ was also investigated. It was observed that ketones react very slowly with $\text{HCo}(\text{CO})_4$ and with very little stereoselectivity.

This project encompassed many aspects of hydrometallation reactions and it has generated more interesting investigations, such as the formation of tertiary amines from aldehydes, ketones or alcohols and the continuing investigations in the areas of carbonylation of metal hydrides and the non-isomerized hydrometallated internal olefins.

During our investigations, we discovered an excellent hydrometallation system which consists of bis-dialkylaminoalanes, $\text{HAL}(\text{NR}_2)_2$, in the presence of a catalytic amount of transition metal halide [e.g. bis-(cyclopentadienyltitanium dichloride, Cp_2TiCl_2]. Since $\text{HAL}(\text{NR}_2)_2$ compounds can be prepared by the reaction of aluminum metal, hydrogen and

dialkylamine in a one step reaction in quantitative yield, and since the resulting compounds are soluble in hydrocarbon solvents as well as ethers, these hydrometallating agents should be both versatile and economically attractive.

Table 8. Reactions of 1-Octene with $\text{HA}(\text{NPr}^1_2)_2$ in the Presence of 5 Mole Percent Catalyst and Quenched with D_2O .^a

CATALYST	OCTANE (%) ^b	% DEUTERIUM ^c INCORPORATION
TiCl_3	95	65
TiCl_4	97	80
VCl_3	10	0
CrCl_3	5	0
MnCl_2	3	0
FeCl_2	5	0
FeCl_3	7	0
CoCl_2	99	10
NiCl_2	99	10
Cp_2TiCl_2	99	93
Cp_2ZrCl_2	5	95
$\text{CpNi}(\text{dep})\text{Cl}$	99	5
$\text{Ni}(\text{acac})_2$	5	0
$\text{Ni}(\text{PEt}_3)_2\text{Br}$	90	7
$\text{Allyl-Ni}(\text{dep})\text{Br}$	81	10
Polymer bound Benzyl- titanocene dichloride	99	0
Cp_2VCl_2	15	2
CuI	5	0
ZnBr_2	5	0

- a) All reactions were carried out in benzene at RT for 30 minutes under an argon atmosphere.
- b) Yield of octane ($d_0 + d_1$) was determined by glc using hexane as the internal standard.
- c) Percent deuterium incorporation = $d_1 / (d_0 + d_1) \times 100$ as determined by mass spectroscopy.

Table 9. Reactions of 1-Octene with $\text{HAl}(\text{NPr}_2)_2$ in the Presence of 5 Mole Percent Cp_2TiCl_2 and Quenched with D_2O .

TEMPERATURE (°C)	TIME (min)	SOLVENT	ATMOSPHERE	(%) DEUTERIUM ^b INCORPORATION
RT	60	THF	N_2	78
RT	60	THF	Ar	87
RT	60	Benzene	N_2	88
RT	60	Benzene	Ar	93
40	10	THF	N_2	75
40	10	THF	Ar	85
40	10	Benzene	N_2	88
40	10	Benzene	Ar	93

a) The yield of octane was 99% in all cases.

b) Percent deuterium incorporation = $d_1 / (d_0 + d_1) \times 100$.

Table 10. Reactions of Alkenes with $\text{HAl}(\text{NPr}_2)_2$ and 5 Mole Percent of Cp_2TiCl_2 and Quenched with D_2O .



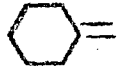

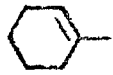

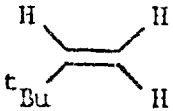
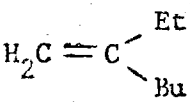
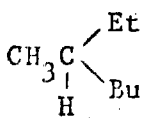
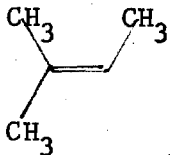
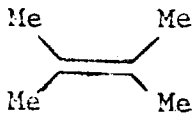
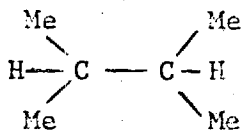
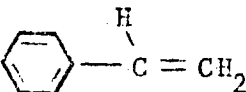
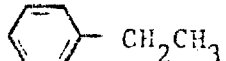
ALKENE	HYDROLYSIS PRODUCT (%) ^b	% DEUTERIUM INCORPORATION ^c
1-Octene ^d	Octane (99)	93
cis-2-hexene	Hexane (99)	83
trans-2-hexene	Hexane (99)	81
	 (47)	20
	 (99)	72
	 (trace)	—
	t-BuCH ₂ CH ₃ (99)	10
	 (90)	75
	2-Methylbutane (trace)	—
	 (0)	—
	 (100) ^e	96 ^e

Table 10. (continued)

- a) All reactions were carried out in benzene at 60°C for 12 hours.
- b) Yield was determined by glc using hexane as the internal standard except for cis- and trans-2-hexene, neohexene and tetramethylethylene when octane was used. The only other compound observed was that of starting material, if any.
- c) Percent deuterium incorporation = $d_1 / (d_0 + d_1) \times 100$ as determined by mass spectroscopy.
- d) Reaction was over in 15 minutes at RT.
- e) 90% of the deuterated ethylbenzene was determined to be PhCH(D)CH_3 with $\text{PhCH}_2\text{CH}_2\text{D}$ accounting for the other 10%.











Table 11. Regioselectivity in the Reaction of $\text{HAL}(\text{NPr}^i)_2$ with Alkenes in the Presence of 5 Mole Percent Cp_2TiCl_2 as Determined by Quenching with a Benzene Solution of Iodine.^a

<u>ALKENE</u>	<u>PRODUCT (%)</u> ^b
1-Octene	1-Iodooctane (80)
1-Hexene	1-Iodohehexane (80)
Cis-2-hexene	1-Iodohehexane (75)
Trans-2-hexene	1-Iodohehexane (75)
3-Hexene	1-Iodohehexane (72) 2 + 3-Iodohehexane (5)

a) All reactions were carried out in benzene for 24 hours at 58°C except for 1-octene which was complete in 15 minutes at RT.

b) Yield was determined by glc using dodecane as the internal standard.

Table 12. Reactions of Dienes with $\text{HA}(\text{NPr}_2)_2$ in THF or Benzene at Room Temperature for 12 Hours in a Diene/ $\text{HA}(\text{NPr}_2)_2$ Ratio of 1:2 and Quenched with D_2O .

DIENE	SOLVENT	RECOVERED DIENE (%) ^a	PRODUCTS (%) ^b	% DEUTERIUM ^c INCORPORATION
	THF	40		60 41
	Benzene	42		58 45
	THF or Benzene	45		55 45
	THF	10		80 10 75 ^d
	Benzene	10		90 90

a) Yields were determined by glc with octane as the internal standard.

b) Yields of products ($d_0 + d_1 + d_2 + \dots$) was determined by glc using octane as the internal standard.

c) By nmr and mass spectroscopy, percent deuterium incorporation = $d_1 / (d_0 + d_1) \times 100$.

d) Percent deuterium incorporation = $d_2 / (d_0 + d_1 + d_2) \times 100$ as determined by mass spectroscopy.

Table 13. Reactions of Cis-2-Hexene and $\text{HA}(\text{NPr}_2)_2$ with Various Catalysts^a and Quenched with a Benzene Solution of Iodine.^{b,c}

CATALYST	CIS-2- HEXENE (%)	TRANS-2- HEXENE (%)	HEXANE (%)	1-iodo HEXANE (%)	2-iodo HEXANE (%)
TiCl_3	20	15	10	55	0
TiCl_4	19	13	12	56	0
VCl_3	93	2	0	0	0
CrCl_3	93	2	5	0	0
MnCl_2	95	3	2	0	0
FeCl_2	70	20	10	0	0
FeCl_3	75	13	12	0	0
CoCl_2	0	1	99	0	0
NiCl_2	0	1	99	0	0
Cp_2ZrCl_2	90	2	5	3	0
Cp_2TiCl_2	8	12	5	75	0
$\text{Cp}_2\text{TiCl}_2^d$	85	15	trace	0	0
$\text{CpNi}(\text{Ph}_3\text{P})\text{Cl}$	3	0	97	trace	0
$\text{Ni}(\text{acac})_2$	90	0	10	0	0
$\text{Ni}(\text{PET}_3)_2\text{Br}_2$	10	0	90	0	0
Allyl Ni(dep)Br	15	0	85	2	0
Cp_2VCl_2	90	3	7	0	0

a) 5 Mole % in benzene

b) All reactions were carried out in benzene at 60°C for 24 hours.

c) Yields were determined by glc with octane as the internal standard and normalized by % cis-2-hexene + trans-2-hexene + hexane + 1-iodohexane + 2-iodohexane = 100%.

d) Reaction was carried out in benzene or THF at RT for 24 hours which was monitored every 3 hours by glc.

Table 14. Reactions of Alkynes with $\text{HAl}(\text{NPr}_2)_2$ and 5 Mole Percent Cp_2TiCl_2 in an Alkyne/Alane Ratio of 1.0:1.02.^a

ALKYNE	WORK UP	PRODUCTS ^b	% YIELD
1-Octyne ^c	D_2O	Octane- d_0 + Octane- d_1 + Octane- d_2 + Octane- d_3	54
		45 22 18 15	
		1-Octene- d_0 + 1-Octene- d_1	46
		22 78	
1-Hexyne ^c	D_2O	Hexane- d_0 + Hexane- d_1 + Hexane- d_2 + Hexane- d_3	49
		41 23 19 17	
		1-Hexene- d_0 + 1-Hexene- d_1	51
		18 82	
2-Octyne	D_2O	Octane- d_0	10
		<u>Cis</u> -2-Octene- d_0 + <u>Cis</u> -2-Octene- d_1	90
		3 97	
		<u>Trans</u> -2-Octene	Trace

Table 14. (Continued)

ALKYNE	WORK UP	PRODUCTS	% YIELD
Hexyl-C \equiv C-SiMe ₃ ^d	D ₂ O	Hexyl-CH ₂ CH ₂ SiMe ₃	5
			87
			90
		10	
		90	
Ph-C \equiv C-Ph	D ₂ O		4
			95

- a) All reactions carried out in benzene at RT for 1 hour and quenched with D₂O or a benzene solution of iodine.
- b) Yields were determined by glc and are based on alkyne and/or octane as the internal standard. The relative ratios of isomers were determined by NMR using benzhydrol as the internal standard.
- c) Reaction carried out at 0°C for 8 hours.
- d) Reaction carried out at 45°C for 12 hours.

Table 15. Reactions of 2-Hexyne with $\text{HAL}(\text{NPr}_2)_2$ and Cp_2TiCl_2 in 1.0:1.02:0.1 Mole Ratio.^a

TIME (hr)	2-HEXYNE RECOVERED (%)	HYDROLYSIS PRODUCTS		TRANS-2- HEXENE (%)	D INCORPOR- ATION (%) ^c
		HEXANE (%)	CIS-2-HEXENE (%)		
0.7	74	7	17	----	-----
1	72	8	20	----	95
2	62	8	30	trace	96
4	53	8	39	trace	95
8	30	8	62	trace	95
16	15	10	73	2	91
16 ^d	0	23	47	30	52

- a) Reactions were carried out in benzene at 0°C under an argon atmosphere and quenched with D_2O .
- b) Yield was determined by glc using octane as the internal standard and normalized (%) 2-hexyne + (%) hexane + (%) cis-2-hexene + (%) trans-2-hexene = 100%.
- c) Percent deuterium incorporation = $d_1 / (d_0 + d_1) \times 100$ as determined by mass spectroscopy.
- d) The temperature was allowed to increase to room temperature.

Table 16. Reactions of 1-Octene with $\text{HAl}(\text{NPr}_2)_2\text{-Cp}_2\text{TiCl}_2$: Effect of Temperature and Catalyst Concentration.

MOLE % Cp_2TiCl_2	TEMPERATURE (°C)	TIME (hr)	OCTANE (%) ^b	D INCORPORATION (%) ^c
5	58	2	100	88
10	58	1	100	83
20	58	0.25	100	86
5	25	12	100	86 ^d
5	25	1.5	10	---

- a) Reactions were carried out in benzene under a nitrogen atmosphere and quenched with D_2O .
- b) Yield was determined by glc using hexane as the internal standard.
- c) Percent deuterium incorporation = $d_1/(d_0 + d_1) \times 100$ as determined by mass spectroscopy.
- d) The percentage of deuterium incorporation increased to 93 when the reaction was conducted under an argon atmosphere and was complete in 15 minutes which was a distinct improvement over the nitrogen experiments.

Table 17. Reactions of the Hydrometallated Species with Carbonyls or Oxygen or Carbon Dioxide in Benzene at Room Temperature for 24 Hours.^a

REAGENT	ADDED CARBONYL	RECOVERED CARBONYL (%)	REDUCED CARBONYL (%)	CARBONYL ADDITION PRODUCT (%)	OTHER PRODUCTS (%)
$\text{HAL}(\text{NPr}_2^i)_2$	Acetone	(35)	(40) Isopropanol	--	-----
	Benzaldehyde	(0)	(100) Benzyl Alcohol	--	-----
	Benzophenone	(0)	(100) Benzhydrol	--	-----
	(THF)	(30)	(45) Axial Alcohol (18) Eq. Alcohol (82)	--	-----
	(Benzene)	(30)	(45) Axial Alcohol (30) Eq. Alcohol (70)	--	-----
$\text{HAL}(\text{NPr}_2^i)_2$ + 1-Octene	Acetone	(70)	(5)	2	-----
	Benzaldehyde	(0)	(10)	Trace $\phi\text{CH}_2\text{NPr}_2^i$	(90)
	Benzophenone	(0)	(35)	Trace $\phi_2\text{CHNPr}_2^i$	(65)
$\text{HAL}(\text{NEt}_2)_2$ + 1-Octene	Acetone	(65)	(5)	2	-----
	Benzaldehyde	(0)	(10)	Trace $\phi\text{CH}_2\text{NEt}_2$	(90)
	Benzophenone	(0)	(38)	Trace $\phi_2\text{CHNEt}_2$	(62)

Table 17. (Continued)

REAGENT	ADDED CARBONYL	RECOVERED CARBONYL (%)	REDUCED CARBONYL (%)	CARBONYL ADDITION PRODUCT (%)	OTHER PRODUCTS (%)
HA1(NPr ⁱ ₂) ₂ + 1-Octene	Acetone	(66)	(5)	1	--
	Benzaldehyde	(0)	(10)	3	$\phi\text{CH}_2\text{NPr}_2^i$ (90)
	Benzophenone	(0)	(37)	3	$\phi_2\text{CHNPr}_2^i$ (63)
HA1(NPr ⁱ ₂) ₂	O ₂	No Reaction			
	CO ₂	No Reaction			

a) Yields for the acetone reactions were determined by glc based on added carbonyl. Yields for the benzaldehyde and benzophenone reactions were determined by NMR using acetone as the internal standard.

Table 18. Reactions of 1-Octene with Substituted Alanes in the Presence of 5 Mole % Cp_2TiCl_2 in Benzene at Room Temperature for 12 Hours.

Alane	Work Up	Product (%) ^a
$\text{HAl}(\text{NPr}_2^i)_2$	I_2	1-Iodooctane (80)
	D_2O	Octane- d_1 (93)
$\text{HAl}(\text{NEt}_2)_2$	I_2	1-Iodooctane (86)
	D_2O	Octane- d_1 (90)
$\text{HAl}[\text{N}(\text{SiMe}_3)_2]_2$	I_2	1-Iodooctane (53) 2-Iodooctane (47)
	D_2O	Octane- d_1 (93)
H_2AlCl	I_2	1-Iodooctane (70)
	D_2O	Octane- d_1 (85)
HAlCl_2	I_2	1-Iodooctane (68)
	D_2O	Octane- d_1 (83)
$\text{H}_2\text{AlOMe}^{b, c}$	I_2	1-Iodooctane (10)
	D_2O	Octane- d_1 (10)
$\text{HAl}(\text{OMe})_2^{b, c}$	I_2	1-Iodooctane (0)
	D_2O	Octane- d_1 (0)
$\text{HAl}(\text{OPr}^i)_2^{c, d}$	D_2O	Octane- d_1 (15)
$\text{HAl}(\text{OBu}^t)_2^{c, d}$	D_2O	Octane- d_1 (15)

a) Yields were determined by glc based upon 1-octene.

b) Insoluble

c) The reagents were prepared in THF but it was removed by vacuum and replaced by freshly distilled benzene. This procedure was repeated three times. According to glc, only 5-10% of THF remained.

d) Slightly soluble

Table 19. Reactions of LiH and Transition Metal Halide with 4-t-Butylcyclohexanone in a 1:1:1 Ratio at Room Temperature for 24 Hours in THF.





TRANSITION METAL HALIDE	AXIAL ^a ALCOHOL (%)	EQUATORIAL ^a ALCOHOL (%)	YIELD (%)
None	45	55	5
CrCl ₃	83	17	8
MnCl ₂	0	0	0
FeCl ₂	0	0	0
CoCl ₂	0	0	0
NiCl ₂	0	0	0
TiCl ₃	61	39	41
VCl ₃ ^c	82	18	86
FeCl ₃	74	26	68
Cp ₂ TiCl ₂	65	35	27
VCl ₃ ^b	80	20	3

a) Yields were determined by glc based on internal standard.

b) Only 5 Mole % of VCl₃ was added.

c) When this reaction was allowed to take place in benzene, an 80% yield of the alcohols was obtained with the axial alcohol consisting 79% of the total.

Table 20. Reactions of Carbonyl Substrates with $\text{LiH}:\text{VCl}_3$ in THF at 45°C for 36 Hours in a Mole Ratio of 1:3.

SUBSTRATE	RECOVERED SUBSTRATE (%)	AXIAL OR EXO ALCOHOL (%) ^a	EQUATORIAL OR ENDO ALCOHOL (%) ^a	YIELD (%)
	11	82	18	86
	3	90	10	90
	0	92	8	90
	3	95	5	95
Benzaldehyde	0	Benzyl Alcohol	97 -----	97
Hexanal	0	Hexanol	95 -----	95
Ethyl Benzoate	0	Benzaldehyde	7 Benzyl Alcohol	93 95
Ethyl Butyrate	0	Butanal	5 Butanol	95 95

a) Yields were determined by glc based on internal standard.

Table 21. Reactions of Alkenes with $\text{LiH}:\text{VCl}_3$ in THF at 45°C for 36 Hours in a Mole Ratio of 1:3 and Quenched with D_2O .

SUBSTRATE	RECOVERED SUBSTRATE (%)	ALKANE (%) ^a	D INCORPORATION (%) ^b
1-Octene	0	Octane (95)	30
<u>Cis</u> -2-Hexene	100	Hexane (0)	-----
<u>Trans</u> -2-Hexene	100	Hexane (0)	-----
2-Ethyl-1-Hexene	5	3-Methylheptane (95)	29
Cyclohexene	100	Cyclohexane (0)	-----
1-Methyl-1-cyclohexene	100	Methylcyclohexane (0)	-----
Methylene-cyclohexane	7	Methylcyclohexane (93)	30

a) Yields were determined by glc based on internal standards.

b) Percent deuterium incorporation = $d_1 / (d_0 + d_1) \times 100$ as determined by mass spectroscopy.

Table 22. Reactions of LiH and NaH with 1-Octene in the Presence of Catalytic Amounts of Transition Metal Halides in Benzene at Room Temperature for 24 Hours and Quenched with D₂O.

METAL HYDRIDE	5 MOLE % CATALYST	RECOVERED 1-OCTENE (%) ^a	OCTANE (%) ^a	D INCORPORATION (%) ^b
LiH	VC1 ₃	94	Trace	-----
	Cp ₂ TiCl ₂	18	77	50
	TiCl ₄	33	59	45
	FeCl ₃	74	25	<5
	NiCl ₂	70	27	<5
	CoCl ₂	65	32	<5
NaH	VC1 ₃	97	0	-----
	Cp ₂ TiCl ₂	94	5	-----
	TiCl ₄	97	Trace	-----
	FeCl ₃	97	0	-----
	NiCl ₂	97	Trace	-----
	CoCl ₂	97	Trace	-----

a) Yields were determined by glc and based on hexane as the internal standard.

b) Percent deuterium incorporation = $d_1 / (d_0 + d_1) \times 100$ as determined by mass spectroscopy.

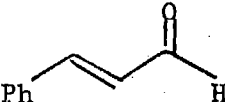
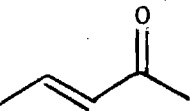
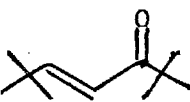
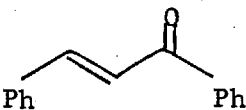
Table 23. Reactions of Alkynes with $\text{LiH}:\text{VCl}_3$ in Benzene at 45°C for 36 Hours in a Mole Ratio of 1:3 and Quenched with D_2O .

SUBSTRATE	RECOVERED SUBSTRATE (%)	ALKANE OR ALKENE (%)	D INCORPORATION (%) ^b
1-Octyne	100	0	0
1-Hexyne	100	0	0
2-Hexyne	100	0	0
1-Phenylpropyne	100	0	0
Diphenylethyne	100	0	0
Phenylethyne	100	0	0

a) Yields were determined by glc and based on an internal standard.

b) Percent deuterium incorporation = $d_1/(d_0 + d_1) \times 100$ as determined by mass spectroscopy.

Table 24. Reactions of Enones with LiH:VCl_3 in Benzene at 45°C for 36 Hours in a Mole Ratio of 1:3.

ENONE	RECOVERED ENONE (%)	1,2-REDUCTION PRODUCT (%) ^a	1,4-REDUCTION PRODUCT (%) ^a	TOTAL REDUCTION (%) ^a
	10	90	0	0
	10	0	0	0
	100	0	0	0
	100	0	0	0

a) Yields were determined by glc based on internal standards.

Table 25. Reactions of Complex Aluminum Hydrides with Olefins and Alkynes in the Presence of 5 Mole % Cp_2TiCl_2 in THF for Two Hours in a Mole Ratio of 1:1 and Quenched with D_2O .^a

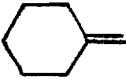
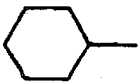
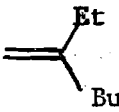
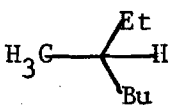

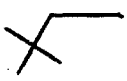


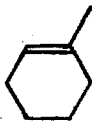
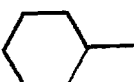
COMPLEX ALUMINUM HYDRIDE	UNSATURATED HYDROCARBON	PRODUCTS (%) ^b	D INCORPORATION (%) ^c
LiAlH_4	1-Octene ^d	Octane (98)	99
	1-Hexene	Hexane (99)	100
	Styrene ^e	Ethylbenzene (70)	100
		 (70)	95
		 (70)	95
		 (60)	55
	<u>Cis</u> -2-Hexene	Hexane (5)	--
	<u>Trans</u> -2-Hexene	Hexane (5)	--
		 (3)	--
		 (0)	--

Table 25. (Continued)

COMPLEX ALUMINUM HYDRIDE	UNSATURATED HYDROCARBON	PRODUCTS (%) ^b	D INCORPORATION (%) ^c
LiAlH_4	1-Octyne	Octane (4)	—
		+	
		1-Octene (3)	—
	Phenylethyne	Styrene (10)	—
		+	
		Ethylbenzene (13)	—
	4-Octyne	<u>Cis</u> -4-Octene (99)	100
	2-Hexyne ^f	<u>Cis</u> -2-Hexene (99)	100
	$\text{Ph-C}\equiv\text{C-Me}$	$\text{PhCH}_2\text{CH}_2\text{CH}_3$ (15)	55
		+	
		$ \begin{array}{c} \text{D} \quad \text{H} \quad \text{H} \quad \text{D} \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{C} = \text{C} \quad + \quad \text{C} = \text{C} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{Ph} \quad \text{Me} \quad \text{Ph} \quad \text{Me} \end{array} $	(70) 95
		90 10	
		+	
		$\text{PhCH}_2\text{CH}=\text{CH}_2$ (15)	85
	$\text{Hexyl-C}\equiv\text{C-SiMe}_3$	$\text{Hexyl-CH}_2\text{CH}_2\text{SiMe}_3$ (15)	20
		+	
		$ \begin{array}{c} \text{Hexyl} \quad \text{SiMe}_3 \\ \diagdown \quad \diagup \\ \text{C} = \text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{H} \end{array} $	(35) 65

Table 25. (Continued)

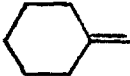
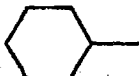
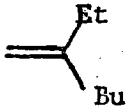
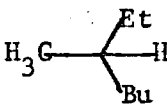




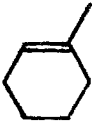
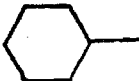
COMPLEX ALUMINUM HYDRIDE	UNSATURATED HYDROCARBON	PRODUCTS (%) ^b	D INCORPORATION (%) ^c
LiAlMe ₃ H	1-Octene ^d	Octane (98)	100
	1-Hexene	Hexane (98)	100
	Styrene ^e	Ethylbenzene (73)	94
		 (69)	94
		 (71)	95
		 (58)	53
	<u>Cis</u> -2-Hexene	Hexane (6)	—
	<u>Trans</u> -2-Hexene	Hexane (5)	—
		 (0)	—
		 (0)	—

Table 25. (Continued)

COMPLEX ALUMINUM HYDRIDE	UNSATURATED HYDROCARBON	PRODUCTS (%) ^b	D INCORPORATION (%) ^c
LiAlMe ₃ H	1-Octyne	Octane (2)	--
		+	
		1-Octene (5)	--
	Phenylethyne	Styrene (9)	--
		+	
		Ethylbenzene (11)	--
	4-Octyne	<u>Cis</u> -4-Octene (100)	100
	2-Hexyne ^f	<u>Cis</u> -2-Hexene (99)	100
	Ph-C≡C-Me	PhCH ₂ CH ₂ CH ₃ (17)	51
		+	
		$ \begin{array}{c} \text{D} \quad \text{H} \quad \text{H} \quad \text{D} \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{C} = \text{C} \quad + \quad \text{C} = \text{C} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{Ph} \quad \text{Me} \quad \text{Ph} \quad \text{Me} \end{array} $ (70) 97	
		90 10	
		+	
		PhCH ₂ CH=CH ₂ (13)	83
	Hexyl-C≡C-SiMe ₃	Hexyl-CH ₂ CH ₂ SiMe ₃ (13)	19
		+	
		$ \begin{array}{c} \text{Hexyl} \quad \text{SiMe}_3 \\ \diagdown \quad \diagup \\ \text{C} = \text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{H} \end{array} $ (34) 65	

Table 25. (Continued)

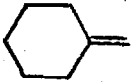
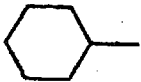
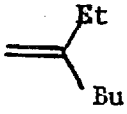
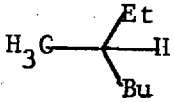
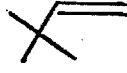
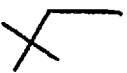


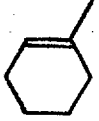
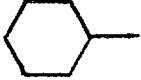
COMPLEX ALUMINUM HYDRIDE	UNSATURATED HYDROCARBON	PRODUCTS (%) ^b	D INCORPORATION (%) ^c
NaAlMe ₃ H	1-Octene ^d	Octane (100)	100
	1-Hexene	Hexane (99)	100
	Styrene ^e	Ethylbenzene (71)	98
		 (69)	93
		 (70)	93
		 (58)	53
	<u>Cis</u> -2-Hexene	Hexane (3)	--
	<u>Trans</u> -2-Hexene	Hexane (3)	--
		 (0)	--
		 (0)	--

Table 25. (Continued)

COMPLEX ALUMINUM HYDRIDE	UNSATURATED HYDROCARBON	^b PRODUCTS (%)	^c D INCORPORATION (%)
NaAlMe ₃ H	1-Octyne	Octane (6)	--
		+	
		1-Octene (6)	--
	Phenylethyne	Styrene (9)	--
		+	
		Ethylbenzene (10)	--
	4-Octyne	<u>Cis</u> -4-Octene (99)	100
	2-Hexyne ^f	<u>Cis</u> -2-Hexene (100)	99
	Ph-C≡C-Me	PhCH ₂ CH ₂ CH ₃ (13)	51
		+	
		$ \begin{array}{ccc} \text{D} & & \text{H} \\ & \diagdown & / \\ & \text{C} = \text{C} & \\ & / & \diagdown \\ \text{Ph} & & \text{Me} \end{array} + \begin{array}{ccc} \text{H} & & \text{D} \\ & \diagdown & / \\ & \text{C} = \text{C} & \\ & / & \diagdown \\ \text{Ph} & & \text{Me} \end{array} \quad (68) $	96
		90 10	
		+	
		PhCH ₂ CH=CH ₂ (19)	86
	Hexyl-C≡C-SiMe ₃	Hexyl-CH ₂ CH ₂ SiMe ₃ (17)	20
		+	
		$ \begin{array}{ccc} \text{Hexyl} & & \text{SiMe}_3 \\ & \diagdown & / \\ & \text{C} = \text{C} & \\ & / & \diagdown \\ \text{H} & & \text{H} \end{array} \quad (30) $	68

Table 25. (Continued)

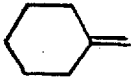
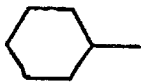
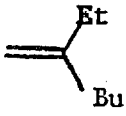
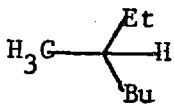
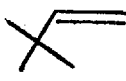
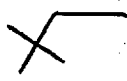


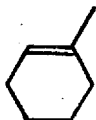
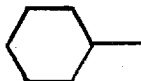
COMPLEX ALUMINUM HYDRIDE	UNSATURATED HYDROCARBON	PRODUCTS (%) ^b	D INCORPORATION (%) ^c
Vitride	1-Octene ^d	Octane (100)	100
	1-Hexene	Hexane (100)	100
	Styrene ^e	Ethylbenzene (72)	99
		 (70)	94
		 (69)	93
		 (59)	51
	<u>Cis</u> -2-Hexene	Hexane (2)	---
	<u>Trans</u> -2-Hexene	Hexane (2)	---
		 (0)	---
		 (0)	---

Table 25. (Continued)

COMPLEX ALUMINUM HYDRIDE	UNSATURATED HYDROCARBON	PRODUCTS (%) ^b	D INCORPORATION (%) ^c
Vitride	1-Octyne	Octane (5)	--
		+	
		1-Octene (6)	--
	Phenylethyne	Styrene (11)	--
		+	
		Ethylbenzene (10)	--
	4-Octyne	<u>Cis</u> -4-Octene (99)	100
	2-Hexyne ^f	<u>Cis</u> -2-Hexene (100)	100
	Ph-C≡C-Me	PhCH ₂ CH ₂ CH ₃ (14)	50
		+	
		$ \begin{array}{ccc} \text{D} & & \text{H} & \text{H} & \text{D} \\ & \diagdown & / & \diagdown & / \\ & \text{C} = \text{C} & + & \text{C} = \text{C} \\ & / & \diagdown & / & \diagdown \\ \text{Ph} & & \text{Me} & \text{Ph} & \text{Me} \end{array} $ (69)	93
		90	10
		+	
		PhCH ₂ CH=CH ₂ (17)	82
Hexyl-C≡C-SiMe ₃		Hexyl-CH ₂ CH ₂ SiMe ₃ (18)	16
		+	
		$ \begin{array}{ccc} \text{Hexyl} & & \text{SiMe}_3 \\ & \diagdown & / \\ & \text{C} = \text{C} \\ & / & \diagdown \\ \text{H} & & \text{H} \end{array} $ (35)	61

Table 25. (Continued)

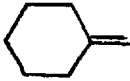
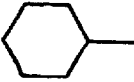
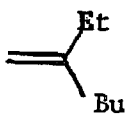
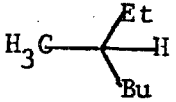
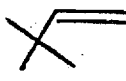
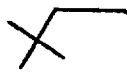


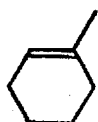
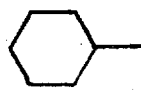
COMPLEX ALUMINUM HYDRIDE	UNSATURATED HYDROCARBON	PRODUCTS (%) ^b	D INCORPORATION (%) ^c
NaAlH ₄	1-Octene ^d	Octane (99)	100
	1-Hexene	Hexane (99)	100
	Styrene ^e	Ethylbenzene (75)	97
		 (71)	94
		 (71)	91
		 (62)	56
	<u>Cis</u> -2-Hexene	Hexane (5)	---
	<u>Trans</u> -2-Hexene	Hexane (5)	---
		 (1)	---
		 (0)	---

Table 25. (Continued)

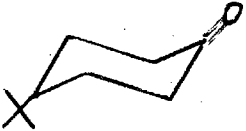

COMPLEX ALUMINUM HYDRIDE	UNSATURATED HYDROCARBON	PRODUCTS (%) ^b	D INCORPORATION (%) ^c
NaAlH ₄	1-Octyne	Octane (4)	--
		+	
		1-Octene (3)	--
	Phenylethyne	Styrene (11)	--
		+	
		Ethylbenzene (15)	--
	4-Octyne	<u>Cis</u> -4-Octene (99)	100
	2-Hexyne ^f	<u>Cis</u> -2-Hexene (98)	100
	Ph-C≡C-Me	PhCH ₂ CH ₂ CH ₃ (8)	50
		+	
		$ \begin{array}{c} \text{D} \quad \quad \text{H} \quad \text{H} \quad \text{D} \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{C} = \text{C} \quad + \quad \text{C} = \text{C} \quad (75) \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{Ph} \quad \quad \text{Me} \quad \text{Ph} \quad \quad \text{Me} \end{array} $	94
		90 10	
		+	
		PhCH ₂ CH=CH ₂ (17)	82
	Hexyl-C≡C-SiMe ₃	Hexyl-CH ₂ CH ₂ SiMe ₃ (18)	18
		+	
		$ \begin{array}{c} \text{Hexyl} \quad \quad \text{SiMe}_3 \\ \diagdown \quad \diagup \\ \text{C} = \text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \quad \text{H} \end{array} \quad (39) $	67

Table 25. (Continued)

COMPLEX ALUMINUM HYDRIDE	UNSATURATED HYDROCARBON	PRODUCTS (%) ^b	D INCORPORATION (%) ^c
$\text{LiAlH}_2(\text{NEt}_2)_2$	1-octene	octane (96)	98
	1-octyne	1-octene (10)	--
		octane (11)	--
	4-octyne	4-octene (95)	97
	cis-2-octene	octane (5)	--
$\text{LiAlH}_2(\text{N}i\text{Pr}_2)_2$	1-octene	octane (92)	96
	1-octyne	1-octene (12)	--
		octane (11)	--
	4-octyne	4-octene (97)	97
	cis-2-octene	octane (2)	--
$\text{NaAlH}_2(\text{NEt}_2)_2$	1-octene	octane (15)	--
	1-octyne	1-octene (15)	--
		octane (13)	--
	4-octyne	4-octene (93)	--
	cis-2-octene	octane (trace)	00
$\text{NaAlH}_2(\text{N}i\text{Pr}_2)_2$	1-octene	octane (95)	96
	1-octyne	1-octene (10)	--
		octane (13)	--
	4-octyne	4-octene (91)	93
	cis-2-octene	octane (2)	--

a) Reaction were carried out in THF at Room Temperature. b) Yields were determined by glc based on internal standards. c) Percent deuterium incorporation = $d_1 / (d_0 + d_1) \times 100$ as determined by mass spectroscopy. d) When the reaction was quenched with a benzene solution of iodine, a 95% yield of only 1-iodooctane was obtained. e) 90% of deuterium was determined to be located on the carbon adjacent to the phenyl ring, PhCH(D)CH_3 . f) When the reaction was quenched with a benzene solution of iodine a 95% yield of a 51:49 ratio of 2-iodo to 3-iodo-cis-2-hexene was obtained.

Table 26. Reaction of Ketones With $\text{HCo}(\text{CO})_4$ at Various Temperatures in Hexane and Ketone: $\text{HCo}(\text{CO})_4$ of 1:2

Ketones	Temperature	Axial Alcohol (%)	Equatorial Alcohol (%)	% Yield ^a
	-22	53	47	3
	0	55	45	2
	RT	53	47	3
	45	53	47	1
	-22	60	40	3
	0	59	41	3
	RT	59	41	2
	45	59	41	1

a) Yields were determined by glc and based on internal standards.

Table 27. Carbonylations of Simple and Complex Metal Hydrides in the Presence of 5 Mole Percent Transition Metal Halides at 4000 psi, Room Temperature, in THF or Hexane for 20 Hours.

<u>METAL HYDRIDE</u> ^a	<u>TRANSITION METAL HALIDE</u>	<u>PRODUCTS</u>
LiH(activated)	none	No Reaction
NaH	TiCl ₄	"
AlH ₃	Cp ₂ TiCl ₂	"
LiAlH ₄	NiCl ₂	"
NaAlH ₄	CoCl ₂	"
	FeCl ₃	"

a) Each metal hydride was allowed to react with each transition metal halide studied.

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PART III

REACTIONS OF MAGNESIUM HYDRIDE:

STEREOSELECTIVE REDUCTION OF CYCLIC AND
BICYCLIC KETONES BY LITHIUM ALKOXYMAGNESIUM HYDRIDES

CHAPTER I

INTRODUCTION

Background

The use of metal hydrides as stereoselective reducing agents in organic chemistry has received considerable attention recently.^{2,3} Although numerous reports have appeared in the literature concerning the reduction of cyclohexanones by hydrides of boron and aluminum, little is known about reductions with magnesium hydride and its derivatives presumably because of the reported lack of reactivity of magnesium hydride and its insolubility in all solvents studied and also because derivatives of magnesium hydride were not known.⁴ Recently, Ashby and co-workers¹ have prepared some THF soluble magnesium-hydrogen compounds of the types HMgOR ⁵ and HMgNR_2 ⁶ which have been shown to exhibit considerable stereoselectivity toward cyclic and bicyclic ketones.⁷ If HMgOR compounds are such good stereoselective reducing agents by virtue of their bulky alkoxy groups, then it would be reasonable to assume that similar "ate" complexes (e.g. alkali metal alkoxymagnesium hydrides) might produce an even greater effect.

Purpose

Reactions of tetrahydrofuran soluble lithium alkoxymagnesium hydrides, $\text{LiMgH}_2(\text{OR})$ ⁸ (where R = methyl, isopropyl, *t*-butyl, neopentyl, cyclohexyl, 2-methylcyclohexyl, phenyl, 2,6-diisopropylphenyl, 2,6-di-*t*-butyl-4-methylphenyl, diphenylmethyl, 2,2,6,6-tetramethylcyclohexyl and

2,2,6,6-tetrabenzylcyclohexyl) with cyclic and bicyclic ketones such as 2-methylcyclohexanone, 4-t-butylcyclohexanone, 3,3,5-trimethylcyclohexanone and camphor have been studied in order to observe any unusual stereoselectivity.

CHAPTER II

EXPERIMENTAL

General Considerations

Reactions were performed under nitrogen or argon at the bench using Schlenk tube techniques⁹ 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.¹⁰ Calibrated syringes equipped with stainless needles were used for transfer of reagents. Glassware and syringes were flamed and cooled under a flow of nitrogen or argon. Ketone, alcohol and internal standard solutions were prepared by weighing the compound in a tared volumetric flask and diluting with the appropriate solvent.

All melting points are corrected. The proton NMR spectra were determined at 60 MHz using a Varian, Model T-60 NMR spectrometer. The chemical shifts are expressed in ppm (δ values) relative to Me_4Si as the 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 & M Model 700 or Model 720 gas chromatograph. The ir spectra were obtained using a Perkin-Elmer, Model 621 or Model 257 infrared spectrometer. High pressure work was conducted in an autoclave (rated to 15,000 psi) obtained from the Superpressure Division of the American Instrument Company.

Analyses

Gas analyses were carried out by hydrolyzing samples with 0.1 M hydrochloric acid on a standard vacuum line equipped with a Toepler pump.⁹ Magnesium was determined by titrating hydrolyzed samples with standard EDTA solution at pH 10 using Eriochrome-Black T as an indicator. Lithium reagents were analyzed by the standard Gilman double titration method (titration of total base followed by titration of total base after reaction with benzyl chloride)¹¹ or by flame photometry. The amount of active C-Mg and C-Li was determined by titrating the active reagent in a dry box with dry 2-butanol in xylene using 2,2'-diquinoline 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. Carbon, hydrogen analyses were carried out by Atlantic Microlab, Inc., Atlanta, Georgia.

Materials

Solvents

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

Fisher reagent grade tetrahydrofuran (THF) was dried over NaAlH_4 and distilled using diphenylmethane as an indicator, under nitrogen, just prior to use.

Fisher reagent grade benzene and hexane 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 argon, just prior to use.

Preparation of 2,2,6,6-tetramethylcyclohexanone

Into a three-necked, 2-l round bottom flask, was placed 24.0 g (0.5 mole) of sodium hydride (50% mineral oil dispersion). The sodium hydride was washed three times with dry hexane by swirling, allowing the hydride to settle, and then decanting the liquid portion in order to remove the mineral oil. The flask was immediately fitted with a magnetic stirrer, a reflux condenser and a pressure-equilizing dropping funnel fitted with a rubber serum cap. A three-way stopcock, connected to the top of the reflux condenser, was connected to a water aspirator and a source of dry argon. The system was evacuated until the last traces of hexane were removed from the sodium hydride and then flushed with argon by evacuating and refilling with nitrogen several times. The aspirator hose was removed and this arm of the stopcock connected to a mineral oil filled bubbler. To the dry sodium hydride was added 250 ml of freshly distilled benzene. Carefully 55 ml (0.5 mole, 44.1 g) of t-amyl alcohol was added to the stirred mixture. The very vigorous reaction was controlled by the drop rate of the alcohol and by a 5-10°C ice-water bath. After addition of the alcohol, an additional 200 ml of alcohol and 100 ml of benzene were added and the ensuing pale brown solution was warmed to room temperature. To this solution was first added 32 ml (0.5 mole, 71.0 g) of iodomethane (Aldrich) and then 10.5 ml (0.10 mole, 9.85 g) of distilled cyclohexanone (Aldrich). The solution turned a bright yellow color and was allowed to stir over night. The reaction mixture was carefully poured into 500 ml of cold water. The mixture was extracted three times with hexane, washed once with water, dried over anhydrous sodium sulfate, filtered and the solvent removed by rotary evaporation. The

crude product was distilled to give 10.5 g (68% yield), b.p. 50-53°C (3 mm) [lit.¹² b.p. 62-65°C (5 mm)]; IR(neat, film) 2950(s), 2920(m), 2860(m), 1700(s), 1470(s), 1390(m), 1370(m), 1040(m); NMR (CDCl₃, TMS) 12H singlet at 1.10 ppm, 6H multiplet at 1.55-1.86 ppm; mass spectrum, m/e (rel. intensity) 154(M⁺, 74), 140(7), 11(7), 83(53), 82(76), 78(18), 72(32), 70(13), 69(65), 57(23), 56(100), 55(62), 41(86).

Anal. Calcd for C₁₀H₁₈O: C, 77.87; H, 11.76. Found: C, 77.81; H, 11.70.

Preparation of 2,2,6,6-tetrabenzylcyclohexanone

The same procedure for preparing 2,2,6,6-tetramethylcyclohexanone was followed. After the formation of sodium t-amylate, 59.5 ml (0.5 mole, 85.50 g) of benzyl bromide was added followed immediately by 10.5 ml (0.10 mole, 9.85 g) of freshly distilled cyclohexanone. The solution turned a grayish white color and was allowed to stir overnight. The reaction mixture was worked up as described above yielding white crystals which upon recrystallization from diethyl ether yielded 15.1 g (33%) of 2,2,6,6-tetrabenzylcyclohexanone, m.p. 155-156°C [lit.¹³ m.p. 155-156°C]; IR (CDCl₃, cavity cell) 3060(w), 3040(w), 3000(m), 2930(s), 2860(w), 1685(s), 1600(m), 1490(s), 1450(s), 1250(s), 860(s); NMR (CDCl₃, TMS) 8H singlet at 1.60 ppm, 6H multiplet at 2.22-2.97 ppm, 20H multiplet at 6.90-7.34 ppm; mass spectrum, m/e (rel. intensity) metastable ion 366.5 (M⁺-92, 35), 277(23), 275(10), 224(34), 91(100).

Anal. Calcd for C₃₄H₃₄O: C, 89.04; H, 7.47. Found: C, 88.90; H, 7.45.

Purification of Alcohols

Methanol (Fisher) was distilled after treating with magnesium metal. Isopropanol (Fisher) was distilled over $\text{Al}(\text{OPr}^i)_3$ and *t*-butyl alcohol (Fisher) was fractionally crystallized under nitrogen. Cyclohexanol, 2-methylcyclohexanol, phenol and 2,6-diisopropylphenol (Ethyl Corporation) were distilled prior to use. Benzhydrol (Aldrich), neopentyl alcohol (Aldrich) and 2,6-di-*t*-butylcresol (Eastman) were used without further purification.

Preparation of 2,2,6,6-tetramethylcyclohexanol

Into a dry 200 ml one-necked round bottom flask equipped with a magnetic stirring bar and a rubber serum cap was placed 10.0 g (0.065 mole) of 2,2,6,6-tetramethylcyclohexanone in 30 ml of distilled diethyl ether. To this stirred solution, cooled by an ice-water bath, was carefully added 45 ml of 1.50 M solution of LiAlH_4 in diethyl ether. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours after which time 20 ml of saturated NH_4Cl solution was added carefully using an ice-water bath to moderate the reaction. The mixture was extracted three times with diethyl ether, washed once with water, dried over anhydrous sodium sulfate, decanted and the solvent removed by rotary evaporation. The crude product was distilled to give 10.0 g (98% yield of 2,2,6,6-tetramethylcyclohexanol, b.p. $54-55^\circ\text{C}$ (3.6 mm) [lit.¹⁴ b.p. $62-65^\circ\text{C}$ (5 mm)]; NMR (CDCl_3 , TMS) 6H singlet at 0.92 ppm, 6H singlet at 0.96 ppm, 6H multiplet at 1.12-1.76 ppm, 1H singlet at 1.92 ppm, 1H singlet at 3.00 ppm; mass spectrum, m/e (rel. intensity) 156(M^+ , 7), 138(13), 123(18), 109(83), 95(15), 82(100), 69(89), 55(44), 43(56), 41(88); IR (CDCl_3 , cavity cell) 3500(broad-m), 2945(s), 2920(m), 2855(m),

1460(s), 1385(m), 1370(m), 1030(m), 850(m).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.78; H, 12.83.

Preparation of 2,2,6,6-tetrabenzylcyclohexanol

The same procedure for preparing 2,2,6,6-tetramethylcyclohexanol was followed. To 15.0 g (0.033 mole) of 2,2,6,6-tetrabenzylcyclohexanone in 30 ml of freshly distilled diethyl ether was added 25 ml of 1.5 M $LiAlH_4$ in diethyl ether. The product was worked up as described above. The yield of 2,2,6,6-tetrabenzylcyclohexanol after being recrystallized twice from diethyl ether, (m.p. 159-160°C; lit.¹⁵ m.p. 161°C) was 10.0 g (66%): IR ($CDCl_3$, cavity cell) 3560(broad-m), 3060(m), 3040(m), 3010(s), 2910(s), 2850(m), 1610(m), 1490(s), 1450(s), 1070(m), 1030(m), 560(m); NMR ($CDCl_3$, TMS) 16H multiplet at 0.72-3.48 ppm, 20H multiplet at 6.70-7.40 ppm; mass spectrum, m/e (rel. intensity) metastable 368.3 ($M^+ - 92, 6$), 211(8), 129(8), 117(7), 115(7), 91(100), 65(10).

Anal. Calcd for $C_{34}H_{36}O$: C, 88.65; H, 7.88. Found: C, 88.55; H, 7.80.

Preparation of Reagents

Solutions of lithium aluminum hydride were prepared by refluxing distilled diethyl ether over solid $LiAlH_4$ (Alfa Inorganics) for 20 hours followed by filtration in the dry box through a fritted glass funnel using dried Celite as a filter aid. The clear solution was standardized for aluminum content by EDTA titration. Diethylmagnesium was prepared by the reaction of diethylmercury¹⁶ with magnesium metal at 60-80°C and a solution in diethyl ether was standardized by magnesium analysis. Lithium hydride was prepared by hydrogenation of t-BuLi or n-BuLi at 4,000 psi

pressure for 24 hours at room temperature. Sodium hydride was obtained as a 50% mineral oil dispersion from Ventron Hydrides Division. Lithium alkoxides were prepared by the reaction of alcohols with n-butyllithium or activated LiH.

Preparation of MgH_2 slurry in THF¹⁷

Lithium aluminum hydride (20 mmole) in diethyl ether (32 ml) was allowed to react with a diethyl ether (50 ml) solution of diethylmagnesium $[(\text{C}_2\text{H}_5)_2\text{Mg}]$ (20 mmole) at room temperature with constant stirring. The reaction mixture was stirred for about 1 hour and the insoluble solid isolated by centrifuging the mixture and then removing the ether solution using a syringe. The resulting solid was washed with freshly distilled diethyl ether and finally a slurry was made by addition of freshly distilled THF.

Anal. Calcd for MgH_2 : Mg:H = 1.00:2.00. Found: 1.00:2.02.

Preparation of Lithium Alkoxymagnesium Hydrides

A known amount of lithium alkoxide in $\text{Et}_2\text{O}/\text{THF}$ was prepared by the reaction of the appropriate alcohol in THF with n-hexane for about 1 hour at room temperature. The lithium alkoxide was allowed to react with a slurry of MgH_2 in THF at room temperature in a 1:1 molar ratio and the reaction mixture stirred for 3-5 hours during which time the MgH_2 dissolved. Analyses of the resulting clear solutions are given in Table 28.

General Reaction of Hydrides With Ketones

A 10 ml Erlenmeyer flask equipped with a Teflon coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen or argon. The flask was then sealed with a rubber serum cap, connected by

means of a syringe needle to a nitrogen/argon filled manifold equipped with a mineral oil filled bubbler. The ketone solutions with internal standard (tetradecane for 4-t-butylcyclohexanone and camphor, hexadecane for 3,3,5-trimethylcyclohexanone and dodecane for 2-methylcyclohexanone) were syringed into the flask and the known concentration of hydride reagent (solution or slurry) added to the flask at room temperature. After the designated time, the reaction was slowly quenched with H₂O and dried over anhydrous MgSO₄. A 10 ft. 5% Carbowax 20 M on Chromosorb W column (130°C column temperature) was used to separate the products of 4-t-butylcyclohexanone, 3,3,5-trimethylcyclohexanone and camphor. A 15 ft. 10% diglycerol on Chromosorb W column (80°C) was used to separate the products of 2-methylcyclohexanone. The order of elution for each ketone was the same: the ketone first, the axial or exo-alcohol second, and the equatorial or endo-alcohol last.

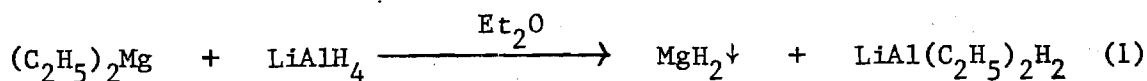
Qualitative Rate Studies of the Reaction of Lithium Alkoxymagnesium Hydrides with 4-t-butylcyclohexanone

The aforementioned conditions for the reduction were set up at the desired temperature. One syringe with the desired amount of ketone and another syringe with a saturated NH₄Cl solution were placed through the rubber serum cap. The ketone was added under an argon atmosphere and at the desired time the reaction was rapidly quenched. The products were analyzed in the normal manner.

CHAPTER III

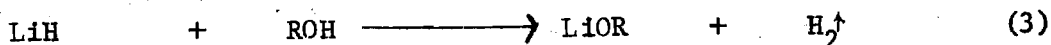
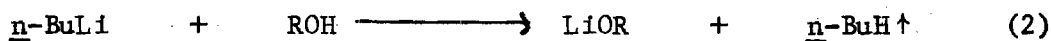
RESULTS AND DISCUSSION

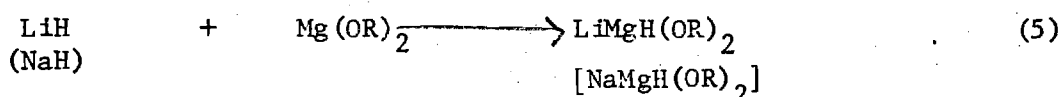
The magnesium hydride used in these studies was prepared by the reaction of $(C_2H_5)_2Mg$ with $LiAlH_4$ in diethyl ether (eq. 1). A slurry of



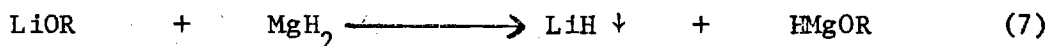
MgH_2 (prepared by this method) in THF was prepared by removing the supernatant solution containing the diethyl ether soluble $LiAl(C_2H_5)_2H_2$ by means of a syring and then adding freshly distilled THF to the resulting diethyl ether-wet solid (MgH_2) several times followed by solvent removal via syring in order to remove the last traces of $LiAl(C_2H_5)_2H_2$.

Magnesium hydride prepared, as described above, was allowed to react with lithium alkoxides (prepared according to equations 2 and 3) in equal molar ratio in THF in order to prepare the desired lithium alkoxymagnesium hydrides (equation 4, Table 28). Lithium dialkoxymagnesium hydrides were prepared according to equation 5 by allowing freshly prepared activated LiH or NaH to react with the appropriate magnesium alkoxide. The magnesium alkoxides were prepared by the reaction of Et_2Mg with freshly distilled alcohol (equation 6).



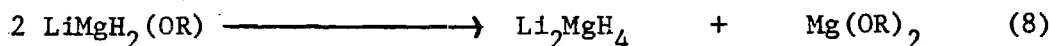


Although MgH_2 is insoluble in THF, a clear solution results in most cases when the lithium alkoxide is allowed to react with the MgH_2 slurry. It is at least theoretically possible that the reaction of lithium alkoxide with MgH_2 proceeds to form THF soluble alkoxy magnesium hydrides (HMgOR)⁵ according to equation 7. However, if this was the case, insoluble LiH



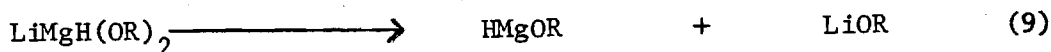
would be formed and yet the reaction gives a clear solution. Thus the possibility of forming HMgOR compounds (eq. 7) does not seem likely.

However, when the solvent of the reaction described by eq. 4 was removed under vacuum and the resulting solid analyzed by x-ray powder diffraction,^{18,19} lines due to magnesium alkoxides were observed suggesting disproportionation (eq. 8) when the solvent is removed. In solution, however, the



integrity of $\text{LiMgH}_2(\text{OR})$ compounds has been confirmed by infrared (Figure 1) and nmr spectral analysis (Figure 2) as well as molecular association stu-

dies reported earlier.^{18,19} Figure 1 shows that in the 1450 cm^{-1} region a distinct absorption occurs for the LiOR compounds whereas it does not appear for the $\text{LiMgH}_2(\text{OR})$, $\text{LiMgH}(\text{OR})_2$ or HMgOR compounds when $\text{R} = 2,2,6,6\text{-tetramethylcyclohexyl}$. However, a shoulder appears for HMgOR and $\text{LiMgH}(\text{OR})_2$ compounds that does not appear for $\text{LiMgH}_2(\text{OR})$ compounds in the 1300 cm^{-1} region. These similarities between HMgOR and $\text{LiMgH}(\text{OR})_2$ compounds could suggest that disproportionation takes place according to equation 9.



However the nmr spectra (Figure 2) show great differences for HMgOR and $\text{LiMgH}(\text{OR})_2$ as well as for LiOR and $\text{LiMgH}_2(\text{OR})$ compounds in the 1.0 ppm region. A broad absorbance is observed for the HMgOR compounds shown in Figure 2, however, for $\text{LiMgH}(\text{OR})_2$ compounds, a much cleaner spectrum is observed in addition to a change in the chemical shift of the two singlets assigned to the methyl groups on the cyclohexyl ring. HMgOR compounds show two singlets at 0.98 and 0.93 ppm, but the singlets associated with the $\text{LiMgH}(\text{OR})_2$ compounds appear at 0.93 and 0.88 ppm. Also, the LiOR compounds have only one singlet at 1.00 ppm, but as noted before, $\text{LiMgH}(\text{OR})_2$ and HMgOR compounds both show two singlets. The NMR were all conducted at the same concentration of reagent in THF-d_8 with Me_4Si as the internal standard with the same resolution. These observations in addition to the molecular association studies reported earlier from this laboratory¹⁸ show the separate identity of these compounds. The molecular weight data show that the HMgOR, $\text{LiMgH}_2(\text{OR})$ and $\text{LiMgH}(\text{OR})_2$ compounds are dimeric in THF.¹⁹ Also it is important to note that the molecular weight

results did not indicate the presence of a mixture of LiOR and HMgOR compounds when the $\text{LiMgH}_2(\text{OR})$ and $\text{LiMgH}(\text{OR})_2$ compounds were being studied.

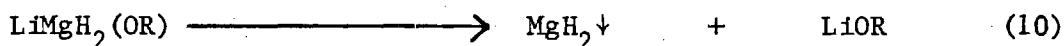
The $\text{LiMgH}_2(\text{OR})$ compounds prepared by the above methods were allowed to react with four representative ketones, i.e., 4-t-butylcyclohexanone (I), 3,3,5-trimethylcyclohexanone (II), 2-methylcyclohexanone (III) and camphor (IV). The purpose of these studies was to evaluate these new hydride reagents as stereoselective reducing agents. We have compared the stereochemical results with that of LiAlH_4 which is considered to be the least sterically hindered hydride that reduces cyclic and bicyclic ketones. For example, LiAlH_4 results in 10, 80, 24 and 9% equatorial or exo attack respectively on ketones I, II, III and IV. On the other hand, MgH_2 reduces ketones I, II, III and IV such that 23, 85, 35 and 8% equatorial or exo attack, respectively, is observed.

Recently, both alkoxymagnesium hydrides $(\text{HMgOR})^{20}$ and dialkylamino-magnesium hydrides $(\text{HMgNR}_2)^{21}$ were prepared in this laboratory. The most selective reagent among the HMgOR compounds studied was 2,6-diisopropylphenoxymagnesium hydride which reduced ketones I, II, III and IV to give 83, 99, 99 and 98% equatorial or endo attack, respectively.²² On the other hand, trimethylsilyl-t-butylaminomagnesium hydride was the most selective HMgNR_2 compound studied. This hydride reduced ketones I, II, III and IV by 73, 99, 98 and 95% equatorial or endo attack, respectively.²³ With these data in hand, the $\text{LiMgH}_2(\text{OR})$ compounds were evaluated on a comparative basis. According to Tables 29-32, lithium dihydrido-2,2,6,6-tetramethylcyclohexoxymagnesiates and lithium dihydrido-2,2,6,6-tetrabenzylcyclohexoxymagnesiates were the most selective in the reduction of ketone (I) (Table 29) providing 89 and 86%, respectively, (Exps. 24 and 25) of the

axial alcohol. When allowed to react with ketone (II) (Table 30), the tetrabenzyl derivative (Exp. 38) produced entirely the axial alcohol. The tetramethyl- and 2-methylcyclohexoxy (Exp. 34) derivatives as well as the neopentyl derivative (Exp. 30) produced 99% of the axial alcohol when allowed to react with the ketone under the same conditions. Both the tetramethyl- and tetrabenzyl- derivatives (Exp. 49 and 50) reduced ketone (III) (Table 31) entirely to the axial alcohol. The neopentyl reagent produced 99% (Exp. 43) of the axial alcohol. When ketone (IV) (Table 32) was reduced, the tetrabenzyl reagent (Exp. 63) again was the most selective providing 99% of the *exo* alcohol. The next best stereoselective reagent was the tetramethyl reagent (Exp. 62) which produced 97% of the *exo*-alcohol.

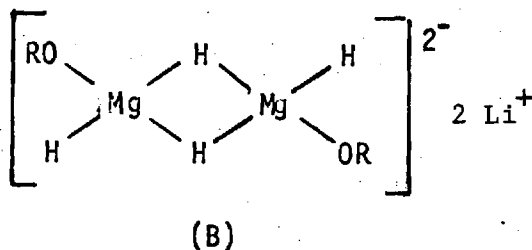
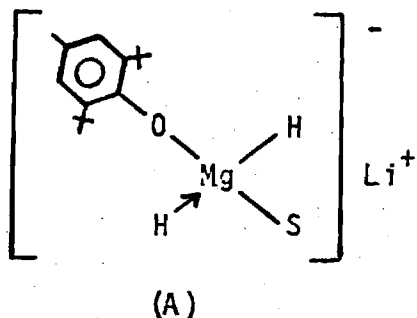
From the data in Table 29, it can be seen that the amount of axial alcohol increases as the steric bulk of the R group increases, particularly when one compares the unsubstituted cyclohexyl derivative (70%) to the 2-methyl derivative (78%), to the tetramethyl derivative (89%). There also is a steady increase in the production of the axial alcohol when proceeding from the primary alkoxy group (OCH_3 , 60%) to the secondary alkoxy groups ($-\text{OPr}^i$ and cyclohexoxy, 70%). As larger secondary groups are introduced into the system (Exps. 17, neopentyl and 18, benzhydryl) the amount of axial alcohol increased even further to 76%. These results support the theory of steric approach control that predicts greater approach of the reagent from the least hindered side of the substrate as the steric requirement of the reagent increases. It is interesting to note that the phenoxy reagents produced less axial alcohol as the steric bulk increased (Exps. 20, 22 and 23). The unsubstituted phenoxy reagent reduced ketone (I) with almost the same stereoselectivity as MgH_2 (Exp. 13).

As diisopropyl and di-t-butyl groups were introduced in the phenoxy system the amount of axial alcohol increased to only 50 and 59%, respectively. Another observation along the same line shown the tertiary derivative (Exp. 16) is not as selective as expected. One might assume from these observations that a small equilibrium amount of MgH_2 is formed by disproportionation (eq. 10) and that a significant portion of the reduction takes



place with MgH_2 . This is not unreasonable since the large steric bulk of the alkoxy group should cause the hydride reagent to react very slowly with the ketones studied thus allowing sufficient time for a competing side reaction (eq. 10) to become significant.

Another explanation of the stereochemical results is that compounds such as $\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_5)$ exist as a monomer (A) and $\text{LiMgH}_2(\text{OPr}^i)$ exists as a dimer (B). This is a reasonable suggestion based on past findings²⁴ that very large alkoxy groups are poor bridging groups compared to smaller alkoxy groups. This suggestion has been confirmed by molecular association studies.¹⁸ In a monomer such as (A) it is clear that attack by a ketone



is less sterically hindered than on the dimer (B). It is likely that reduction takes place by displacement of the solvent (S) from (A) which should take place easier than the breaking of the Mg-H bond of the dimer (B) in order to produce a coordination site.

When these same lithium alkoxymagnesium hydrides were allowed to react with ketone (II), 3,3,5-trimethylcyclohexanone (Table 30), the tetra-benzyl derivative (Exp. 38) produced only the axial alcohol. Again the phenoxy and the diisopropylphenoxy (Exps. 33 and 35) derivatives produced the axial alcohol in almost the same yield as did MgH_2 40% versus 85% (Exps. 26 and 33). The di-t-butylphenoxy derivative (Exp. 36) also produced a lesser amount (93%) of the axial alcohol than expected. These results can also be explained by assuming disproportionation of the reagent to MgH_2 as suggested earlier or by assuming differences in molecular aggregation of the reagents. The other derivatives produced similar results with respect to each other and therefore no trends are readily recognizable.

The reduction of 2-methylcyclohexanone (Table 31) with $\text{LiMgH}_2(\text{OR})$ compounds produced the same trends described earlier for 4-t-butylcyclohexanone (Table 29). We once again observed the same low yield of axial alcohol for the unsubstituted phenoxy derivative (Exp. 46, 38%) compared to MgH_2 (Exp. 39, 35%). The other phenoxy derivatives (Exps. 47, 66% and 48, 67%) as well as the tertiary butyl derivative (Exp. 42, 67%) produced less axial alcohol than expected which is presumably due to reduction of the ketone by a small equilibrium amount of MgH_2 formed through disproportionation of the reagent (eq. 10) which would lower the stereoselectivity of the reagent. Again, there is an increase in selec-

tivity when proceeding from the primary methoxy group (Exp. 40, 71%) to the secondary isopropoxy (Exp. 41, 96%) or cyclohexoxy (Exp. 45, 96%) group of the reagent. As noted before, increasing the steric bulk in the primary alkoxy reagents, i.e. neopentoxy (Exp. 43), or for the secondary alkoxy reagents i.e. benzhydryloxy (Exp. 44) also increased the production of the axial alcohol to 96%.

The reactions of these lithium alkoxymagnesium hydrides with camphor (Table 32) produced similar trends as noted for the previous reaction except for the dramatic differences observed for the methoxy (Exp. 52, 12%), *t*-butoxy (Exp. 54, 10%), neopentoxy (Exp. 55, 9%) and cyclohexoxy (Exp. 57, 15%) reagents. These reagents produced amounts of endo-alcohol greater than MgH_2 (Exp. 51, 8%) alone. This observation implies that the above hydrides have less steric requirement when approaching camphor than MgH_2 . This is entirely possible. Other than the observations just mentioned the trends described earlier seem to be followed for camphor as well. An increase in stereoselectivity is observed as the steric requirement of the reagent increases: cyclohexoxy (Exp. 57, 15% endo-alcohol) < 2-methylcyclohexoxy (Exp. 59, 7% endo-alcohol) < 2,2,6,6-tetramethylcyclohexoxy (Exp. 62, 3% endo-alcohol) < 2,2,6,6-tetrabenzylcyclohexoxy (Exp. 63, 1% endo-alcohol). The phenoxy derivatives (Exps. 58, 8%; 60, 8%; 61, 7% endo-alcohol) provided the same selectivity as MgH_2 (8% endo alcohol) for presumably the same reasons described earlier.

Another interesting observation is that the cyclohexoxy reagent shows the lowest yield of alcohols (Exps. 19, 45, and 57) for the reduction of ketones I, III and IV but not in the case of ketone (II) (Exp. 32).

Evidently enolization should be much greater in the case of ketone I, III and IV because of the greater steric hindrance in the case of ketone (II). Why enolization is greater for the cyclohexoxy derivative compared to the other hydrides is not clear. It should also be noted that all of the phenoxy derivatives provide the highest yields even though the stereoselectivity is less than the other hydrides. In general, it appears that all of the reagents capable of producing small amounts of MgH_2 , as described above, produced the least amount of enolization. Magnesium hydride itself produced a 100%⁵ yield of the reduction products with all of the ketones studied except for ketone (II) (Exp. 26). Ketone (II) is the ketone which the cyclohexoxy reagent did not enolize the ketone (Exp. 32) at all. However, it should also be noted that for the reduction of ketone (II) another secondary alkoxy reagent (benzhydroyloxy) did have the most enolization associated with it (Exp. 31). The reason why MgH_2 or very bulky reagents lower the amount of enolization is probably due to steric reasons.

It was also desired to determine if the degree of stereoselectivity was higher in the initial stages of the reaction than after equilibrium had been reached. In this connection, 4-t-butylcyclohexanone was allowed to react with a 100% excess of 2,2,6,6-tetrabenzoxoydihydridomagnesi-ate. The results are give in Table 33 and Figure 3. As can be seen from the data, the lower the temperature, the greater the observed enolization to reduction ratio. At -25°C , for example, the major product (64%) after quenching is the starting ketone, 4-t-butylcyclohexanone. It should also be noted that the initial reaction is very fast and that after 5 hours no more than a 5% change was observed in the ratio of alcohols. The thermo-

dynamic product is the equatorial alcohol, and if 4-t-butylcyclohexanone is allowed to react under equilibrium conditions inherent for Meerwein-Ponndorf-Verley or Birch reductions, the equatorial alcohol is produced in 98-99% yield.²⁵ For lithium alkoxymagnesium hydride reductions, never less than 86% of the axial alcohol is observed. It appears that most of the stereochemical composition always takes place during the time between 60 and 18,000 seconds indicating some, but slow equilibrium.

Tables 34-37 list the results of the reactions of ketones (I), (II), (III) and (IV) with lithium dialkoxymagnesium hydrides prepared according to equation 5. The most selective reagents were the bis-tetramethyl- and bis-tetrabenzylcyclohexoxy hydrides (Exps. 67a and 68a) which reduced ketone (I) (Table 34) to provide 89 and 85% axial alcohol, respectively. However a large amount of enolization accompanied the reaction (66 and 60%, respectively). On the other hand, Exp. 65a shows that the bis-di-t-butyl derivative enolized only 18% of the ketone while reducing the ketone to 81% of the axial alcohol. The sodium reagent (Exp. 66a) not only produced a 55:45 axial to equatorial alcohol ratio, but also enolized 85% of the ketone. When LiH and LiOR were allowed to react under similar conditions (Exp. 64a) a 74:26 ratio of axial to equatorial alcohol was observed but 70% of the ketone was enolized.

When ketones (II), (III) and (IV) (Tables 35-37) were allowed to react with these reagents, lesser amounts of enolization were observed with very stereoselective results. All the reagents studied produced 99% to 100% axial alcohol when allowed to react with ketones (II) and (III) (Tables 35 and 36, respectively). The reactions with camphor (ketone IV, Table 37) produced greater than 90% exo-alcohol with little enolization

except for Exps. 64d and 66d which produced 65 and 62% respectively of the starting ketone. These reagents represent a method of using lithium and sodium hydride for reduction which has not been previously reported, and further development is now under way.

CHAPTER IV

CONCLUSION








A series of lithium alkoxymagnesium hydrides, $\text{LiMgH}_2(\text{OR})$, were prepared and allowed to reduce 4-t-butylcyclohexanone (I), 3,3,5-trimethylcyclohexanone (II), 2-methylcyclohexanone (III) and camphor (IV). It was found that very bulky secondary cyclic alkoxy groups such as 2,2,6,6-tetramethyl- or benzylcyclohexoxy were very stereoselective in the reduction of these ketones. For example, $\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_4\text{C(CH}_3)_3)$ reduced ketone (I) to provide 89% of the axial alcohol compared to $\text{HMgO}-\text{C}_6\text{H}_4\text{C(CH}_3)_3$ which provided 83% of the axial alcohol.

The $\text{LiMgH}(\text{OR})_2$ when $\text{R} = \text{C}_6\text{H}_4\text{C(CH}_3)_3$ or C_6H_5 reagents were also found to reduce ketones (I), (II), (III) and (IV) stereoselectively but to a lesser extent and with more enolization than observed for the $\text{LiMgH}_2(\text{OR})$ reagents.

Table 28. Preparation of Lithium Alkoxy-magnesium Hydrides $[\text{LiMgH}_2(\text{OR})]$ by the Reaction of Magnesium Hydride with Lithium Alkoxides in a 1:1 Ratio.

Exp.	Reaction Time (hr)	Solubility in THF	Analysis (Ratio)				Product
			Li	: Mg	: H	: ROH	
1	10	Insoluble	1.05	1.00	1.91	1.02	$\text{LiMgH}_2(\text{OCH}_3)$
2	7	Soluble	1.04	1.00	1.93	1.01	$\text{LiMgH}_2(\text{OPr}^1)$
3	7	Soluble	1.04	1.00	1.93	1.03	$\text{LiMgH}_2(\text{OBu}^t)$
4	6	Soluble	1.03	1.00	1.95	1.02	$\text{LiMgH}_2(\text{OCH}_2\text{Bu}^t)$
5	8	Soluble	1.04	1.00	1.92	1.02	$\text{LiMgH}_2(\text{OCHPh}_2)$
6	7	Soluble	1.00	1.02	1.95	1.03	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_{11})$
7	8	Insoluble	1.03	1.02	1.90	1.04	$\text{LiMgH}_2(\text{OPh})$
8	5	Soluble	1.02	1.00	1.96	1.00	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_{11})$
9	7	Soluble	1.03	1.00	1.92	1.03	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_4)$
10	6	Soluble	1.02	1.02	1.94	1.00	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_4)$
11	5	Soluble	1.01	1.01	1.96	1.00	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_{11})$
12	5	Soluble	1.01	1.01	1.97	1.00	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_4)$

Table 29. Reaction of 4-t-Butylcyclohexanone with LiMgH₂(OR) Compounds at Room Temperature in THF Solvent.

Exp.	Hydride	Relative Yield (%) ^a		Yield(%) ^b
		Axial-OH	Equatorial-OH	
13	MgH ₂	23	77	100
14	LiMgH ₂ (OCH ₃)	60	40	95
15	LiMgH ₂ (OPr ⁱ)	70	30	91
16	LiMgH ₂ (OBu ^t)	59	41	98
17	LiMgH ₂ (OCH ₂ Bu ^t)	76	24	95
18	LiMgH ₂ (OCHPh ₂)	76	24	90
19	LiMgH ₂ (O- )	70	30	52
20	LiMgH ₂ (O- )	28	72	100
21	LiMgH ₂ (O- )	78	22	83
22	LiMgH ₂ (O- )	50	50	100
23	LiMgH ₂ (O- )	59	41	99
24	LiMgH ₂ (O- )	89	11	86
25	LiMgH ₂ (O- )	86	14	85

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

b) Yield was determined by glc and based on an internal standard.

Table 30. Reactions of 3,3,5-Trimethylcyclohexanone with $\text{LiMgH}_2(\text{OR})$ Compounds at Room Temperature in THF 1:2 Molar Ratio.

Exp.	Hydride	Relative Yield ^a		Yield ^b
		Axial-OH	Equatorial-OH	
26	MgH_2	85	15	92
27	$\text{LiMgH}_2(\text{OCH}_3)$	95	5	93
28	$\text{LiMgH}_2(\text{OPr}^i)$	98	2	84
29	$\text{LiMgH}_2(\text{OBu}^t)$	96	5	100
30	$\text{LiMgH}_2(\text{OCH}_2\text{Bu}^t)$	99	1	88
31	$\text{LiMgH}_2(\text{OCHPh}_2)$	97	3	80
32	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_{11})$	96	4	100
33	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_5)$	90	10	100
34	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_4\text{CH}_3)$	99	1	100
35	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_3(\text{CH}_3)_2)$	90	10	100
36	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_2(\text{CH}_3)_3)$	93	7	100
37	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_4\text{C(CH}_3)_3)$	99	1	100
38	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_2(\text{CH}_3)_3\text{C(CH}_3)_3)$	100	0	96

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

b) Yield was determined by glc using an internal standard.

Table 31. Reactions of 2-Methylcyclohexanone with $\text{LiMgH}_2(\text{OR})$ Compounds at Room Temperature in THF Solvent in 1:2 Ratio.

Exp.	Hydride	Relative Yield (%) ^a		Yield(%) ^b
		Axial-OH	Equatorial-OH	
39	MgH_2	35	65	100
40	$\text{LiMgH}_2(\text{OCH}_3)$	71	29	94
41	$\text{LiMgH}_2(\text{OPr}^{\text{i}})$	96	4	92
42	$\text{LiMgH}_2(\text{OBu}^{\text{t}})$	67	33	100
43	$\text{LiMgH}_2(\text{OCH}_2\text{Bu}^{\text{t}})$	99	1	88
44	$\text{LiMgH}_2(\text{OCHPh}_2)$	98	2	88
45	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_{11})$	96	4	78
46	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_5)$	38	62	100
47	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_4\text{CH}_3)$	66	34	100
48	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_3\text{CH}_3)$	67	33	95
49	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_4\text{CH}_2\text{CH}_3)$	100	0	87
50	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_4\text{CH}_2\text{CH}_2\text{CH}_3)$	100	0	85

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

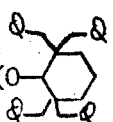
b) Yield was determined by glc using an internal standard.

Table 32. Reactions of Camphor with $\text{LiMgH}_2(\text{OR})$ Compounds at Room Temperature in THF Solvent in 1:2 Molar Ratio.

Exp.	Hydride	Relative Yield (%) ^a		Yield (%) ^b
		Endo-OH	Exo-OH	
51	MgH_2	8	92	100
52	$\text{LiMgH}_2(\text{OCH}_3)$	12	88	88
53	$\text{LiMgH}_2(\text{OPr}^i)$	8	92	100
54	$\text{LiMgH}_2(\text{OBu}^t)$	10	90	91
55	$\text{LiMgH}_2(\text{OCH}_2\text{Bu}^t)$	9	91	100
56	$\text{LiMgH}_2(\text{OCHPh}_2)$	4	96	100
57	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_{11})$	15	85	52
58	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_5)$	8	92	100
59	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_4)$	7	93	83
60	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_3)$	8	92	100
61	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_2)$	7	93	100
62	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_1)$	3	97	95
63	$\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_0)$	1	99	95

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

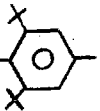
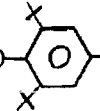
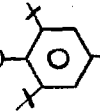
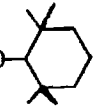
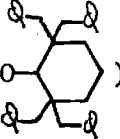
b) Yield was determined by glc using an internal standard.

Table 33. The Reaction of LiMgH_2 () in THF Solvent with 4-t-Butyl-Cyclohexanone at Various Temperatures and Reaction Times in 2:1 Molar Ratio.

TEMP. °C	TIME (sec)	Recovered Ketone (%)	Axial ^a Alcohol (%)	Equatorial ^a Alcohol (%)
-25°	2	75	91	9
	5	70	90	10
	10	67	90	10
	15	67	90	10
	30	66	90	10
	18,000	64	86	14
0	2	75	90	10
	5	67	91	9
	10	56	90	10
	15	47	90	10
	30	37	89	11
	45	37	88	12
	18,000	35	86	14
RT	2	76	90	10
	5	65	90	10
	10	47	91	9
	15	38	92	8
	30	22	91	9
	45	15	89	11
	60	15	89	11
	18,000	15	86	14

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

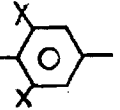
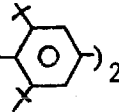
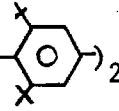
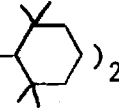
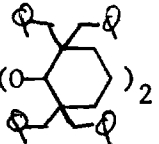
Table 34. Reactions of 4-t-Butylcyclohexanone with Metal Hydrides and Magnesium Alkoxide at Room Temperature in THF Solvent and in 1:2 Molar Ratio for 24 Hours.

Exp.	Reagent	Recovered Ketone (%)	Reduction Products		Yield (%) ^b
			Axial Alcohol (%) ^a	Equatorial Alcohol (%) ^a	
64a	LiH + LiO- 	70	74	26	28
65a	LiH + Mg(O- ) ₂	18	81	19	80
66a	NaH + Mg(O- ) ₂	85	55	45	10
67a	LiH + Mg(O- ) ₂	66	89	11	30
68a	LiH + Mg(O- ) ₂	60	85	15	37

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

b) Yield was determined by glc using an internal standard.

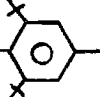
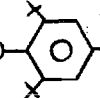
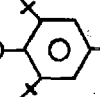
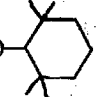
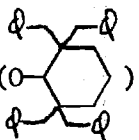
Table 35. Reactions of 2-Methylcyclohexanone with Metal Hydrides and Magnesium Alkoxides at Room Temperature in THF Solvent and in 1:2 Molar Ratio for 24 Hours.

Exp.	Reagent	Recovered Ketone (%)	Reduction Products		Yield (%) ^b
			Axial Alcohol (%) ^a	Equatorial Alcohol (%) ^a	
64b	LiH + LiO- 	--	--	--	--
65b	LiH + Mg(O- ) ₂	14	99	1	85
66b	NaH + Mg(O- ) ₂	--	--	--	--
67b	LiH + Mg(O- ) ₂	30	99	1	65
68b	LiH + Mg(O- ) ₂	35	99	1	60

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

b) Yield was determined by glc using an internal standard.

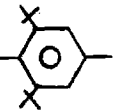
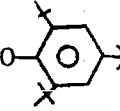
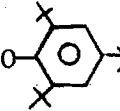
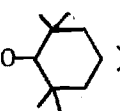
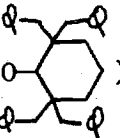
Table 36. Reactions of 3,3,5-Trimethylcyclohexanone with Metal Hydrides and Magnesium Alkoxides at Room Temperature in THF Solvent and in 1:2 Molar Ratio for 24 Hours.

Exp.	Reagent	Recovered Ketone (%)	Reduction Products		Yield (%) ^b
			Axial Alcohol (%) ^a	Equatorial Alcohol (%) ^a	
64c	LiH + LiO- 	--	--	--	--
65c	LiH + Mg(O- ) ₂	8	100	0	90
66c	NaH + Mg(O- ) ₂	--	--	--	--
67c	LiH + Mg(O- ) ₂	35	100	0	60
68c	LiH + Mg(O- ) ₂	42	100	0	55

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

b) Yield was determined by glc using an internal standard.

Table 37. Reactions of Camphor with Metal Hydrides and Magnesium Alkoxides at Room Temperature in THF Solvent and in 1:2 Molar Ratio for 24 Hours.

Exp.	Reagent	Recovered Ketone (%)	Reduction Products		Yield (%) ^b
			Axial Alcohol (%) ^a	Equatorial Alcohol (%) ^a	
64d	LiH + LiO- 	65	91	9	30
65d	LiH + Mg(O- ) ₂	0	95	5	100
66d	NaH + Mg(O- ) ₂	62	90	10	36
67d	LiH + Mg(O- ) ₂	11	97	3	87
68d	LiH + Mg(O- ) ₂	16	96	4	81

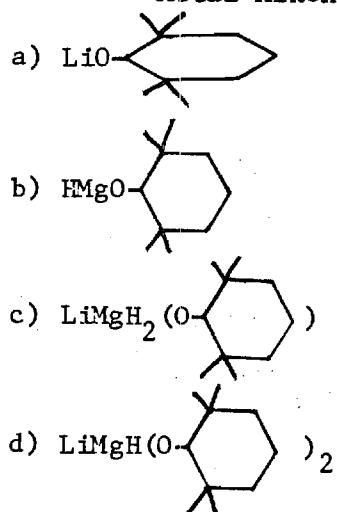
a) Normalized % axial alcohol + % equatorial alcohol = 100%.

b) Yield was determined by glc using an internal standard.

FIGURE 1

IR Spectra of Simple and Complex

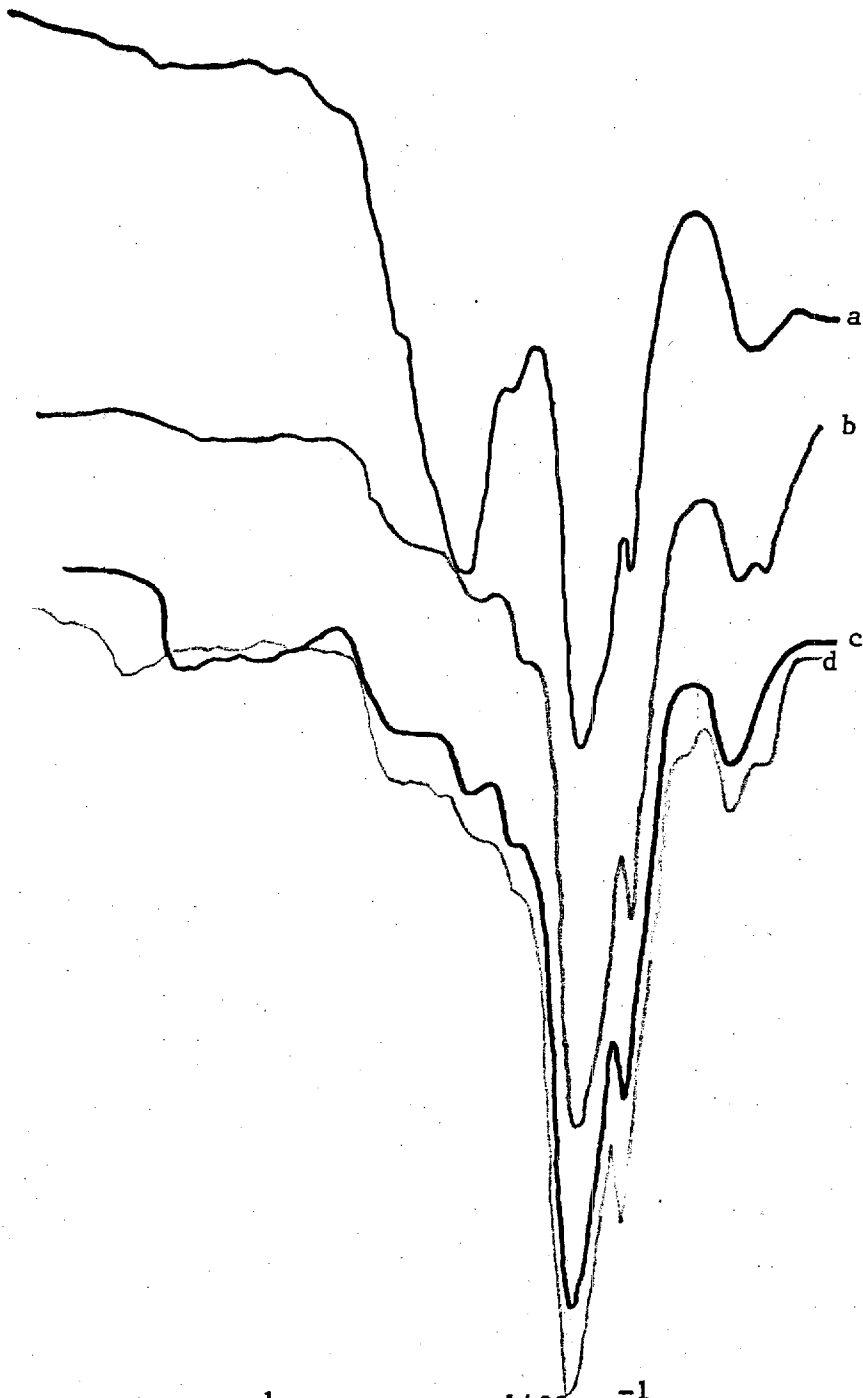
Metal Alkoxides



1600 cm^{-1}

1400 cm^{-1}

1200 cm^{-1}



1600 cm^{-1}

1400 cm^{-1}

1200 cm^{-1}

FIGURE 2

NMR Spectra of Simple and Complex
Metal Alkoxides

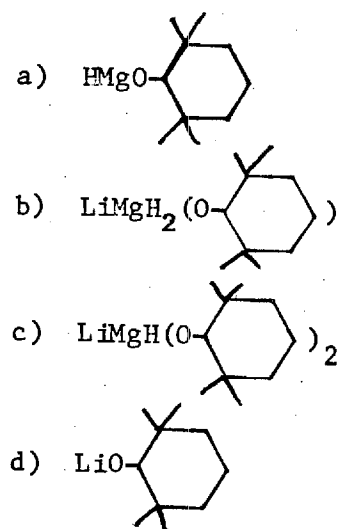




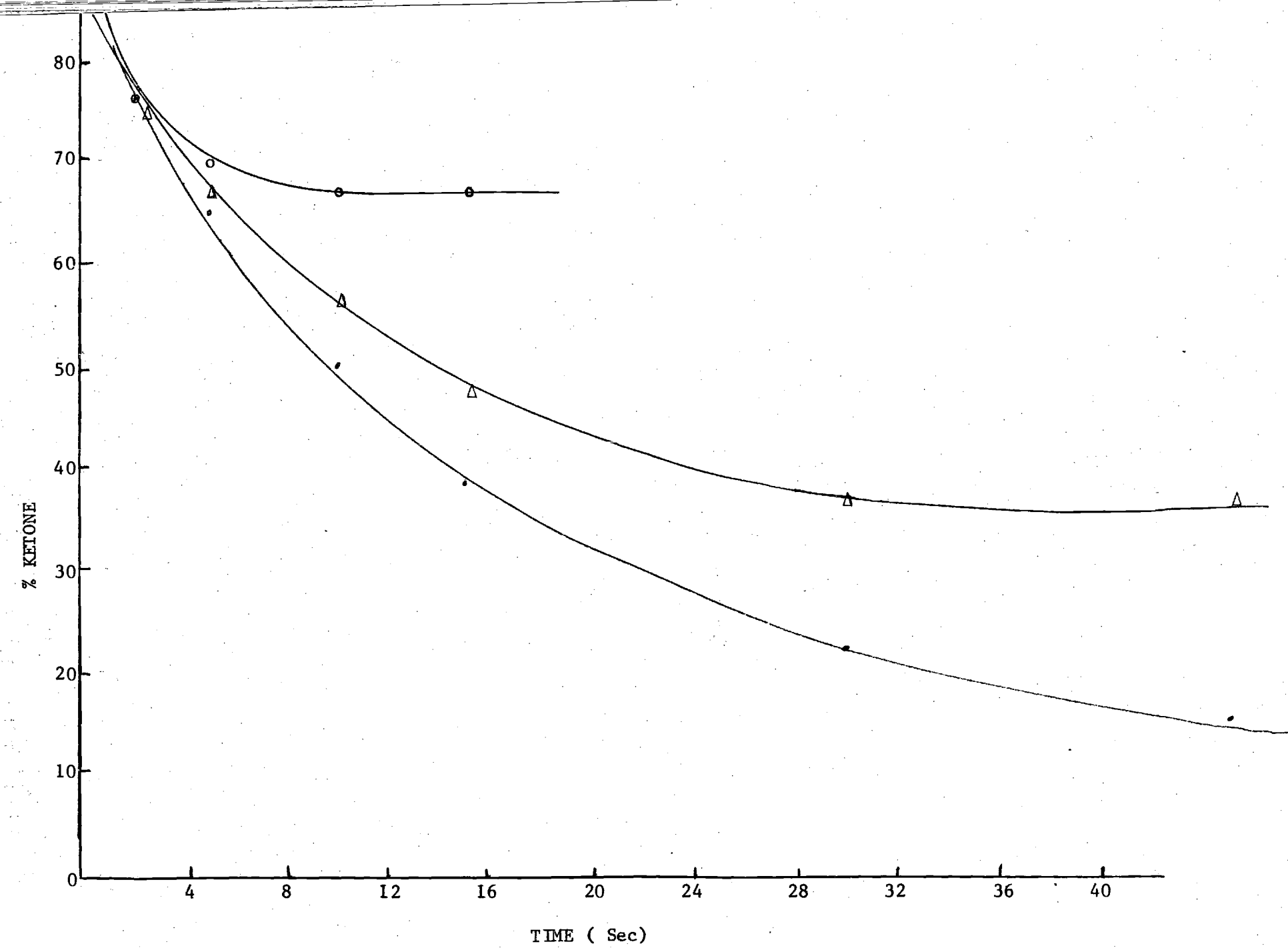
FIGURE 3

The Reaction of $\text{LiMgH}_2(\text{O}-\text{C}_6\text{H}_{10})$
in THF with 4-t-butylcyclohexanone in 2:1 Ratio

o -25°C

Δ 0°C

. RT (25°C)



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PART IV

CONCERNING SALT EFFECTS ON THE STEREOSELECTIVITY OF
ORGANOMETALLIC COMPOUND ADDITION TO KETONES

CHAPTER I

INTRODUCTION

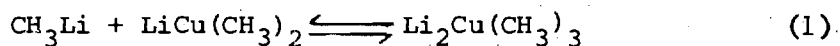
Background

Recently, it was reported that a mixture of CH_3Li and $\text{LiCu}(\text{CH}_3)_2$ provides unusually high stereoselectivity (94% equatorial attack) in the methylation of 4-tert-butylcyclohexanone compared to reaction of CH_3Li or $\text{LiCu}(\text{CH}_3)_2$ alone.¹ It was suggested that "a bulky, highly reactive cuprate having the stoichiometry $\text{Li}_2\text{Cu}(\text{CH}_3)_3$ or $\text{Li}_3\text{Cu}(\text{CH}_3)_4$ " was formed when CH_3Li and $\text{LiCu}(\text{CH}_3)_2$ are allowed to react; and, reaction of these cuprates with the ketone would explain the observed results. However, molecular weight measurements indicate that $\text{Li}_2\text{Cu}(\text{CH}_3)_3$ is monomeric in diethyl ether and THF, whereas CH_3Li is tetrameric and $\text{LiCu}(\text{CH}_3)_2$ is dimeric. As a monomer, $\text{Li}_2\text{Cu}(\text{CH}_3)_3$ should not be considered more bulky than a tetrameric molecule such as CH_3Li . Reactions of $\text{Li}_2\text{Cu}(\text{CH}_3)_3$, $\text{LiCu}(\text{CH}_3)_2$ and $\text{LiCu}_2(\text{CH}_3)_3$ in both diethyl ether and THF with selected enones indicates that $\text{Li}_2\text{Cu}(\text{CH}_3)_3$ is only slightly more reactive than $\text{LiCu}(\text{CH}_3)_2$ toward conjugate addition.⁵ Therefore, the hypothesis that $\text{Li}_2\text{Cu}(\text{CH}_3)_3$, when present in a mixture of CH_3Li and $\text{LiCu}(\text{CH}_3)_2$ in diethyl ether, is a "bulky, highly reactive cuprate" is questionable.

The CH_3Li - $\text{LiCu}(\text{CH}_3)_2$ mixture used to methylate 4-tert-butylcyclohexanone was prepared by reacting CH_3Li with CuI in a 8:3 molar ratio in diethyl ether solvent. In such a mixture at least three species are present: $\text{LiCu}(\text{CH}_3)_2$, CH_3Li and LiI . The reaction of any

one of these compounds with 4-tert-butylcyclohexanone fails to produce the unusual stereochemistry reported above. One can suggest four possible explanations for this stereoselectivity: (1) CH_3Li reacts with $\text{LiCu}(\text{CH}_3)_2$ to form a complex which then reacts with the ketone;¹ (2) CH_3Li reacts with LiI to form a complex (a reaction known to produce $\text{Li}_4(\text{CH}_3)_3\text{I}$)² which then reacts with the ketone; (3) $\text{LiCu}(\text{CH}_3)_2$ and LiI react to form a complex which then reacts with the ketone; (4) one of the species in solution reacts with the ketone to form a complex followed by reaction of the complexed carbonyl compound with CH_3Li .

Recently, low temperature ¹H NMR evidence⁶ was reported for the existence of $\text{Li}_2\text{Cu}(\text{CH}_3)_3$ in a mixture of CH_3Li and $\text{LiCu}(\text{CH}_3)_2$ in dimethyl ether, tetrahydrofuran and diethyl ether solvents. No evidence was found to indicate the presence of any higher order complexes, such



as $\text{Li}_3\text{Cu}(\text{CH}_3)_4$. The reaction CH_3Li - $\text{LiCu}(\text{CH}_3)_2$ with 4-tert-butylcyclohexanone in THF did not yield any increased stereoselectivity when compared to CH_3Li alone. Since Ashby, et al. have determined that $\text{Li}_2\text{Cu}(\text{CH}_3)_3$ exists in both ether and THF and is monomeric in both solvents,² it is doubtful that $\text{Li}_2\text{Cu}(\text{CH}_3)_3$ would react with 4-tert-butylcyclohexanone in diethyl ether to give unusual stereoselectivity when in THF no trace of unusual stereoselectivity is observed. Therefore, one is led to question that the observed stereoselectivity in diethyl ether is due to the reaction of $\text{Li}_2\text{Cu}(\text{CH}_3)_3$ with the ketone.

The stereochemical improvement in the CH_3Li - $\text{LiCu}(\text{CH}_3)_2$ reagent

in diethyl ether cannot be explained by assuming that a complex between CH_3Li and LiI (formed in the reaction of CH_3Li with CuI) is reacting with the ketone. A mixture of CH_3Li and LiI or LiBr (Table 11) while giving some improvement in stereoselectivity, does not give the selectivity observed with the $\text{CH}_3\text{Li-LiCu}(\text{CH}_3)_2$ mixture. Also, a mixture of CH_3Li and LiI or LiBr in THF gives no improvement in stereoselectivity over CH_3Li alone. It is known that CH_3Li forms complexes with both LiI and LiBr in THF.⁷ Likewise, the stereochemical improvement cannot be explained by assuming that a complex between either $\text{LiCu}(\text{CH}_3)_2$ or $\text{Li}_2\text{Cu}(\text{CH}_3)_3$ and LiI is reacting with the ketone, since a halide free mixture of CH_3Li and $\text{LiCu}(\text{CH}_3)_2$ gives the same high stereoselectivity

The only reasonable possibility remaining then is that CH_3Li reacts with a complex between $\text{LiCu}(\text{CH}_3)_2$ and ketone (eq. 2). This



suggestion also explains why there is no rate enhancement or increase in stereoselectivity when the same reaction is conducted in THF; i.e., the ketone would not be expected to compete effectively with THF solvent molecules for coordination sites on lithium. The unusual rate enhancement in diethyl ether is explained on the basis that the concentration of ketone complexed to $\text{LiCu}(\text{CH}_3)_2$, LiI , et. would be expected to be considerably higher in ether than in THF and certainly the complexed carbonyl compound would be much more reactive than the uncomplexed carbonyl. Recent reports involving ^{13}C NMR have confirmed that no

complex formation exists between CH_3Li and lithium salts such as LiClO_4 ,⁷ but complex formation does take place between LiClO_4 and the carbonyl group^{7,8} in diethyl ether and yet as stated earlier, a dramatic increase in stereoselectivity is observed with LiClO_4 just as in the case of $\text{LiCu}(\text{CH}_3)_2$.

Purpose

In order to complete a more detailed study of the unusual stereoselectivity found in the alkylation of cyclohexanones with CH_3Li in the presence of lithium salts, several metal salts were added to the reaction of CH_3Li and 4-t-butylcyclohexanone. In an attempt to expand the scope of the reaction, other ketones (e.g. 2-methyl- and 3,3,5-trimethylcyclohexanone) and other organolithium reagents (e.g. t-butyl- and phenyllithium) were also allowed to react in the presence of LiClO_4 . Similar studies were also conducted with organomagnesium and aluminum reagents in place of CH_3Li .

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(II) oxide 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 flamed and cooled under a flow of nitrogen or argon. Ketones, metal salts and solutions of internal standards were prepared by weighing the reagent in a tared volumetric flask and diluting with the appropriate solvent. GLPC analyses were carried out on an F and M Model 700 or Model 720 gas chromatograph. Flame photometry was conducted on a Coleman Model 21 Flame Photometer.

Analyses

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

followed by titration of residual base after reaction with benzyl chloride)¹¹ or by flame photometry. 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.

Materials

Tetrahydrofuran (Fisher Certified Reagent Grade) was distilled under nitrogen from NaAlH_4 and diethyl ether (Fisher Reagent Grade) from LiAlH_4 prior to use. Methyllithium in THF or diethyl ether was prepared by the reaction of $(\text{CH}_3)_2\text{Mg}$ with excess lithium metal dispersion (Alfa), 30% in petrolatum, which was washed repeatedly with ether/pentane until clean under an argon atmosphere prior to use. Both solutions were stored at -78°C until ready to use.

Dimethylmagnesium was prepared¹² by the reaction of dimethylmercury with magnesium metal (ROC/RIC) at $40-60^\circ\text{C}$ in the absence of solvent. The resulting $(\text{CH}_3)_2\text{Mg}$ was extracted from the gray solid with ether and the resulting solution standardized by magnesium analysis.

Trimethylaluminum (Ethyl Corporation) was distilled under vacuum in a glove box and standard solutions were prepared in diethyl ether and THF. The resulting solutions were standardized by aluminum and methane analysis.

Lithcoa's t-butyllithium and n-butyllithium, MC/B methyllithium and PCR Incorporated phenyllithium were analyzed prior to use for active C-Li by the Watson and Eastman procedure described in the Analytical Section. The methyllithium reagent was also analyzed by methane gas analysis using standard vacuum line techniques. All reagents were hydrolyzed prior to use and the organic fractions subjected to glpc analysis.

LiAlH_4 (Alfa Inorganic) was suspended in refluxing ether or THF for

24 hours, then filtered in a glove box using a glass fritted funnel and Celite filter aid. The clear solutions were standardized by aluminum and gas analyses prior to use.

Alane, AlH_3 , in THF or diethyl ether was prepared by the reaction of 100% H_2SO_4 with LiAlH_4 in the appropriate solvent¹³ at -78°C followed by filtration of the resulting Li_2SO_4 in the dry box. Analysis:

$\text{Li}:\text{Al}:\text{H} = 0.02:1.00:3.00$.

Camphor, norcamphor, 2-methylcyclohexanone, 3,3,5-trimethylcyclohexanone and 4-t-butylcyclohexanone were obtained from Aldrich Chemical Company or Chemical Samples Company and sublimed or distilled and stored over 4A molecular sieves prior to use.

Lithium salts: lithium perchlorate, lithium iodide and lithium bromide were purchased from Alfa Inorganics and dried under vacuum at 100°C overnight.

Sodium tetraphenyl borate and tetramethylammonium iodide were purchased from Fisher and used without further purification.

Lithium methoxide and t-butoxide were prepared by the reaction of n-butyllithium in hexane with a stoichiometric amount of the appropriate alcohol under anhydrous conditions using an argon atmosphere.

Magnesium methoxide and t-butoxide as well as bis-diisopropylaminomagnesium were prepared in diethyl ether by the reaction of dimethylmagnesium with a stoichiometric amount of the appropriate alcohol or amine under an argon atmosphere.

Aluminum methoxide and isopropoxide and tris-diisopropylaminoaluminum were prepared in THF by the reaction of alane with a stoichiometric amount of the appropriate alcohol or amine under an argon atmosphere.

If the lithium, magnesium or aluminum salts were desired in another solvent, the original solvent was removed by vacuum and replaced by the desired solvent which was freshly distilled. This procedure was repeated three times.

General Reactions of Ketones

A 10 ml Erlenmeyer flask with a teflon coated magnetic stirring bar was dried in an oven and allowed to cool under argon or nitrogen. The flask was then sealed with a rubber serum cap and connected by means of a syringe needle to an argon or nitrogen filled manifold. The amount of organometallic reagent (ca. 0.1-1.0 mmole) in THF or diethyl ether was added to the flask using a syringe, and the addition of the metal salt solution followed, if needed. The temperature was controlled by a dry ice-acetone bath, then the calculated amount of ketone in THF or diethyl ether was added to the stirred mixture.

The reverse addition (organometallic reagent added to a mixture of ketone, internal standard and metal salt at -78°C) produced the same results. After the designated time, the reaction was quenched with the slow addition of methanol and dried over anhydrous MgSO_4 . A 12 ft. 20% FFAP on Diatoport S column (column temperature: 150°C , helium flow rate: 60 ml/min) was used to separate the products of 4-t-butylcyclohexanone. The retention time was 13.0 minutes for $n\text{-C}_{14}\text{H}_{30}$, 33.0 minutes for cis-1-methyl-4-t-butylcyclohexanol, 38.0 minutes for 4-t-butylcyclohexanone and 41.5 minutes for trans-1-methyl-4-t-butylcyclohexanol. A 14 ft. 10% diglycerol on Diatoport S column at 80°C was used to separate the products of 2-methylcyclohexanone. The retention time was 4.4 minutes for the ketone, 5.2 minutes for the cis-alcohol, 9.5 minutes for the trans-alcohol

and 16.1 minutes for $n\text{-C}_{14}\text{H}_{30}$. A 10 ft. column of 20% SAIB on Chromosorb W at 180°C and flow rate of 60 ml/minute gave the following retention times for ketone, axial alcohol and equatorial alcohol for the methylation of 3,3,5-trimethylcyclohexanone: 5.0, 4.3 and 6.0 minutes.

The isomeric alcohols resulting from the methylation of norcamphor could not be separated by glpc. In addition, the isomeric alcohols resulting from the phenylation of all ketones studied could not be determined by glpc because of dehydration. Therefore, the isomer ratios in these cases were determined by NMR analysis. Ashby, Laemmle and Roling¹⁴ determined the methyl singlet for the resulting exo-alcohol from the methylation of norcamphor to be 73 Hz in benzene and the endo-alcohol methyl group singlet to be 74 Hz. These results were confirmed by the author.

The identification of the phenylation products of all ketones was determined by NMR spectroscopy utilizing the peak areas of the hydroxyl protons of the alcohols in DMSO-d_6 . In these cases, work up of reaction mixtures was carried out as follows. After the reaction was complete, distilled water was added in order to effect hydrolysis. The solution was then transferred to a separatory funnel and washed several times with distilled water. The ether layer was separated and allowed to evaporate and DMSO-d_6 added to the sample. The sample was then dried over Linde 4A molecular sieves and transferred to an NMR tube. This procedure minimized dehydration and equilibration. Benzaldehyde was added as the internal standard.

In the case of phenylation of 4-t-butylcyclohexanone, the chemical shifts for the axial and equatorial hydroxyl protons are 4.56 ppm and 4.73 ppm respectively. The assignment of each alcohol hydroxyl peak to a

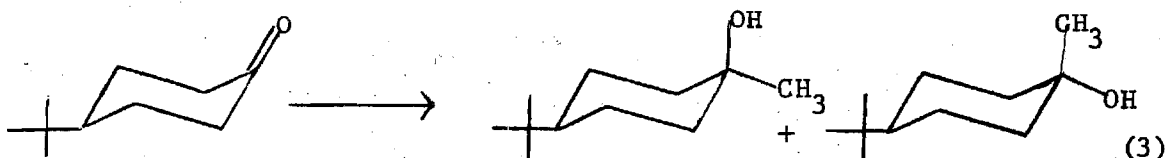
particular isomer was based on several reports in the literature concerning their chemical shifts in DMSO and DMSO-d₆.¹⁵ The identification of the phenylation products of 2-methylcyclohexanone was accomplished according to the procedure of Luderer, Woodall and Pyle.¹⁶ The ¹H NMR showed the methyl doublet of the axial alcohol to be at 0.60 ppm and the methyl doublet associated with the equatorial alcohol to be at 0.62 ppm. Identification of the t-butylation products of 4-t-butylcyclohexanone was accomplished according to the method of Meakins, et al.^{15c} The axial hydroxyl proton in DMSO-d₆ is 3.49 ppm. Finally, the identification of the t-butylation products of 2-methylcyclohexanone was accomplished by the method of Ficine and Maujean.¹⁷

CHAPTER III

RESULTS AND DISCUSSION

Organolithium Reactions

The detailed results of stereoselective methylation in diethyl ether of 4-t-butylcyclohexanone (eq. 3) by main group metal organometallic



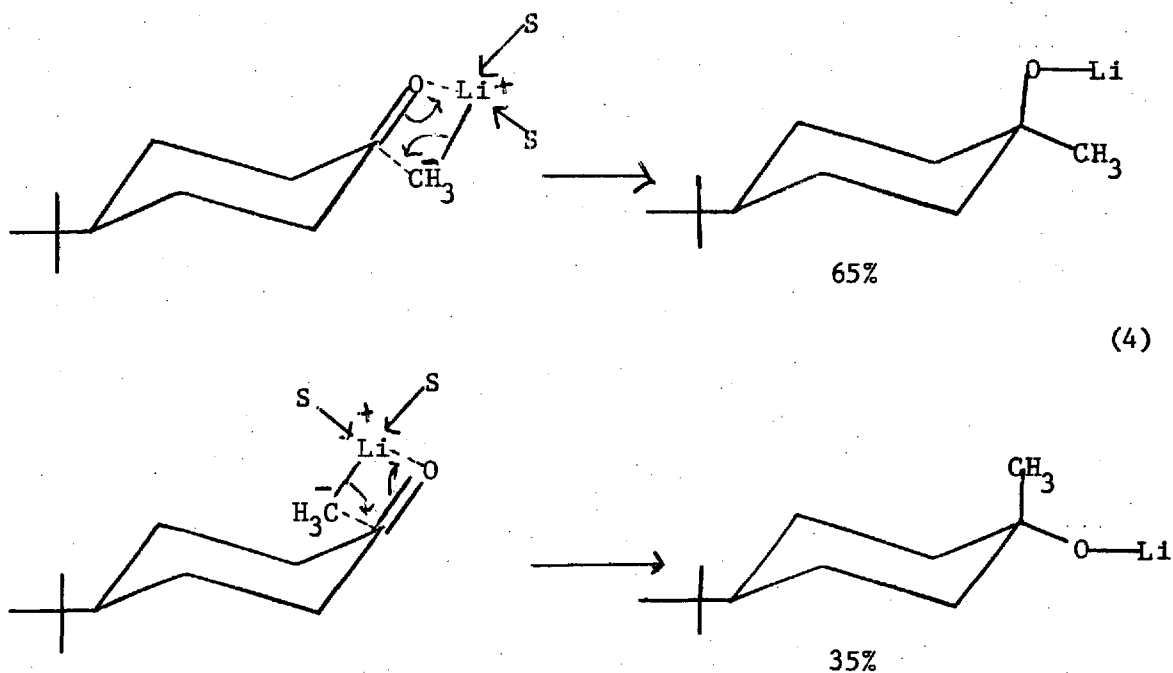
reagents in the presence of equimolar amounts of various metallic salts [ca. LiBr, LiI, LiClO₄, NaBPh₄, Me₄NI, LiOBu^t, Mg(OPrⁱ)₂, Al(OPrⁱ)₃ and Al(NPrⁱ)₃] are reported in Tables 38, 45 and 47. When CH₃Li was allowed to react with 4-t-butylcyclohexanone in diethyl ether solvent, 65% of the axial alcohol was formed. However, when LiOBu^t, LiBr,¹⁸ LiI¹⁸ or LiClO₄¹⁸ (Table 38) was added to an ether solution of CH₃Li before it was added to the ketone, the amount of axial alcohol formed increased to 75, 76, 81 or 92% respectively. When THF was substituted for diethyl ether, no increase in stereoselectivity was observed. A number of other salts (Exps. 2-7) produced no effect or only a slight increase (~5%) in the formation of axial alcohol. For the cases when Al(NPrⁱ)₃, Al(OPrⁱ)₃, Mg(OCH₃)₂, Mg(OPrⁱ)₂ and LiOBu^t were present, the total product yield decreased to 80, 85, 83, 85 and 73 % respectively. This compares to the

total product yield \geq 92% for the other reactions. This result is presumably due to enolization.

Because LiClO_4 had the greatest effect on the stereochemistry of this reaction, it was decided to study the scope of this reaction using LiClO_4 but varying the nature of the ketone and the organolithium reagent.

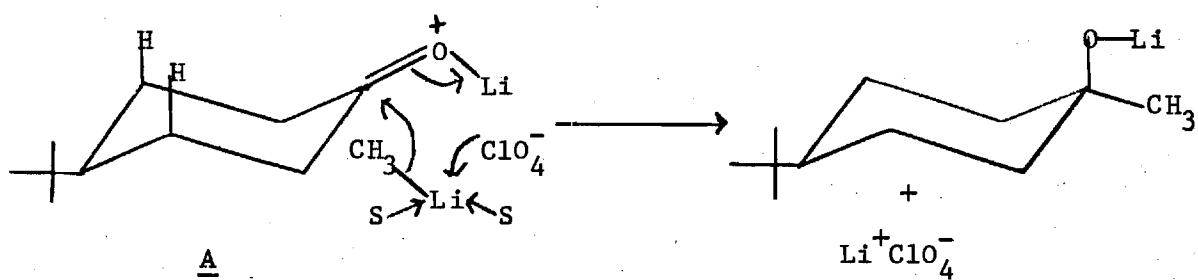
When ketones other than 4-t-butylcyclohexanone (Table 39) were allowed to react with CH_3Li in the presence of LiClO_4 , only 2-methylcyclohexanone showed a modest increase in the production of the axial alcohol (88% without and 96% with LiClO_4 added). The other ketones, 3,3,5-trimethylcyclohexanone and norcamphor did not show any increase in the formation of the axial alcohol since only the axial or endo-alcohol was observed in the absence of LiClO_4 . However, even these ketones showed a pronounced rate enhancement when allowed to react with CH_3Li in the presence of LiClO_4 (Table 40). In the absence of LiClO_4 , the reaction of CH_3Li with 4-t-butylcyclohexanone, 2-methylcyclohexanone or norcamphor was essentially over in one hour; however, when LiClO_4 was present, the reaction was complete in less than 10 seconds at -78°C . The substantial rate enhancement is probably due to the increased reactivity of the newly formed complex between the carbonyl group and LiClO_4 (eqs. 4 and 5).

Equation 4 illustrates the proposed transition state for the reaction of CH_3Li with 4-t-butylcyclohexanone which provides 65% of the axial alcohol upon hydrolysis.

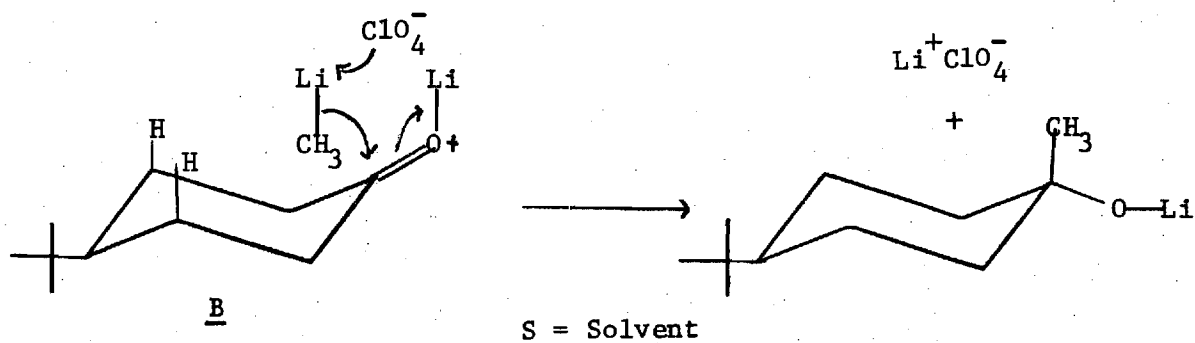


(4)

If LiClO_4 is introduced (eq. 5), complexation between LiClO_4 and



(5)



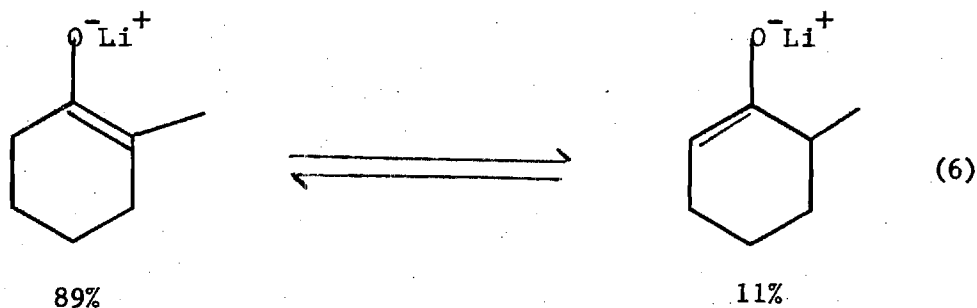
the carbonyl group takes place increasing the rate of subsequent attack by CH_3Li and also influencing the subsequent stereochemistry of the reaction. It is not surprising that complexation between LiClO_4 and the carbonyl group increases the rate of reaction with CH_3Li since the complexed carbonyl group should be highly polarized as in other cases of acid catalysis of carbonyl compounds. This complexation also accounts for the increase in the formation of the axial alcohol because complex A does not have the 3,5-diaxial hydrogen interaction as illustrated in complex B. The complexation also explains the results obtained when THF is the solvent: namely, no rate enhancement or increase in the stereoselectivity. THF is more basic than diethyl ether and therefore the carbonyl group can no longer compete for complexation of LiClO_4 .

When phenyllithium was allowed to react with 4-t-butylcyclohexanone and 2-methylcyclohexanone (Tables 41 and 42, respectively) in the presence of an equimolar amount of LiClO_4 in diethyl ether, only a slight increase in the formation of the axial alcohols were observed compared to the reaction without LiClO_4 . When t-butyllithium was allowed to react with the same two ketones in the presence of LiClO_4 , no change in stereochemistry was observed since 100% axial alcohol was already formed in the absence of LiClO_4 . It was hoped that by increasing the steric requirements in the transition state (eq. 5) some reversal of stereochemistry would ensue for those ketones which provided 100% of one alcohol isomer. For example, the alkylation of norcamphor with CH_3Li provides 100% of the endo-alcohol, but camphor provides 100% of the exo-alcohol presumably due to the increased steric hindrance of camphor's methyl groups encountered with exo attack. Unfortunately, the t-butyllithium reagent

proved to be so bulky that the presence or absence of LiClO_4 is irrelevant.

An interesting observation concerning the reaction of t-butyllithium with 4-t-butylcyclohexanone in the absence of LiClO_4 is that of the products formed, 7% was the equatorial alcohol produced by reduction of the ketone (Exp. 47) and 30% was recovered ketone. On the other hand, in the presence of LiClO_4 , the reduction product was only 1%, but the amount of recovered ketone increased to 37%. From Table 43 it can be seen that without the addition of LiClO_4 (Exp. 38), the reaction is essentially over in 15 minutes, but in the presence of LiClO_4 (Exp. 39), the reaction is over in less than 5 seconds. Evidently, the complexation of the ketone with LiClO_4 increases the rate of the addition reaction substantially without affecting the β -hydrogen reduction pathway and hence, 1,2-addition product increases relative to reduction product in the presence of LiClO_4 .

When t-butyllithium was allowed to react with 2-methylcyclohexanone (Table 42, Exps. 34 and 35), 13% of the ketone was recovered in the absence of LiClO_4 and 14% of the ketone was recovered when an equal molar amount of LiClO_4 was present. When comparing this result with that of the 4-t-butylcyclohexanone reaction, it is noticed that 30% of 4-t-butylcyclohexanone is recovered when LiClO_4 is not present. An explanation of this result can be given in terms of enolization intermediates. 4-t-Butylcyclohexanone has four hydrogen atoms available for abstraction with the two equatorial ones being the most accessible. 2-Methylcyclohexanone has three hydrogens available for abstraction, but the most stable enolate predominates in an 89:11 ratio (eq. 6)¹⁹. Based on this, it is expected that the 4-t-butylcyclohexanone would have



roughly twice as many hydrogens available for abstraction than 2-methylcyclohexanone, and this is indeed reflected in the amounts of recovered starting ketones for the two reactions (30:13) after hydrolysis.

As discussed above, it was also observed that only the axial alcohol, cis-1,2-dimethylcyclohexanol, was produced whether LiClO_4 was present or not. But, just as for the 4-t-butylcyclohexanone reaction (Table 43), the presence of LiClO_4 enabled the reaction to be complete in less than 5 seconds for presumably the same reasons discussed above.

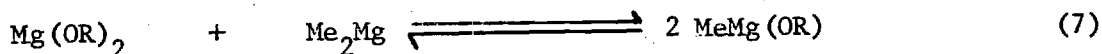
When phenyllithium was allowed to react with 4-t-butylcyclohexanone, 58% of the axial alcohol was produced without the addition of LiClO_4 . When LiClO_4 was added, the percentage of axial alcohol increased to 69%. A similar result was obtained with the reaction of 2-methylcyclohexanone and PhLi . The axial alcohol, cis-1-phenyl-2-methylcyclohexanol, was produced in 88% yield without the addition of LiClO_4 , but with LiClO_4 added, the amount of axial alcohol increased to 94%. Evidently, the reasons discussed for the CH_3Li reactions also hold for the phenyllithium reactions but not to the same degree. An explanation for this maybe due to the fact that CH_3Li exists as a tetramer and phenyllithium as a dimer in diethyl ether. Therefore, the CH_3Li could be considered a

more bulky reagent, and together with the effect of LiClO_4 has a greater effect on the outcome of the addition reactions with ketones than phenyllithium.

Organomagnesium Reactions

Chastrette and Amouroux²⁰ reported that the presence of LiClO_4 or $n\text{-Bu}_4\text{NCl}$ in the reaction of Grignard reagents with 4-t-butylcyclohexanone has no effect on the stereochemistry of the products. Georgoulis et al.²¹ also reported that the presence of KO^tBu has no effect on the stereochemistry of the reaction of R_2Mg compounds with 4-t-butylcyclohexanone; however, it did increase the amount of enolization product. Our work in this area was carried out in order to verify these results as well as investigate the influence of other salts and ketones in the reaction of organomagnesium compounds with cyclohexanones. The results are recorded in Table 44.

In general, we observed only slight increases (4-7%) in the formation of the axial alcohols for the reaction of dimethylmagnesium with ketones in the presence of equal molar amounts of LiClO_4 compared to the reactions in the absence of LiClO_4 . However, for the norcamphor reactions only the endo-alcohol was observed. We also observed that when $\text{Mg}(\text{OPr}^i)_2$ (Table 44, Exp. 48), was present in equal molar ratio with $(\text{CH}_3)_2\text{Mg}$, the stereochemistry of the product increased from 62% axial alcohol when no salt was present (Exp. 42) to 75% (Exp. 48) when salt was present. A similar result was obtained when MeMgOPr^i was allowed to react with the same ketone. Therefore it maybe argued that a redistribution reaction according to equation 7 took place which accounts for the so called salt effect.



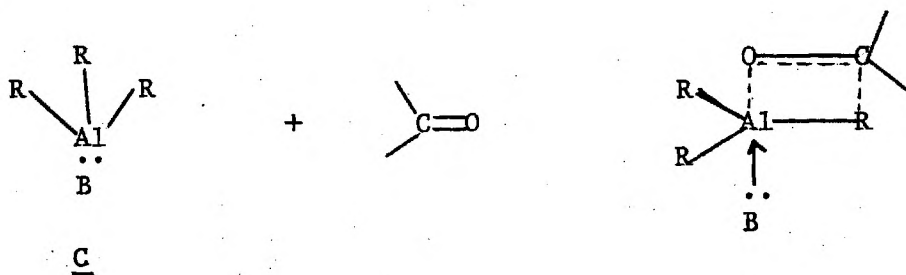
Other salts, NaBPh₄, LiBr or LiI, did not produce any different results than the reactions carried out in the absence of salt. LiOBu^t did not increase the stereoselectivity of the reaction, but it did increase the amount of enolization (30%) (Exp. 47) as was observed by Georgoulis²¹ using KOBu^t.

Of the alcohols produced from the reactions of 4-t-butylcyclohexanone, 3,3,5-trimethylcyclohexanone and 2-methylcyclohexanone with (CH₃)₂Mg in the absence of LiClO₄, 62, 85 and 80% were the respective axial or cis-alcohols. With LiClO₄ present, the amount of axial or cis-alcohols increased to 69, 89 and 84%, respectively (Table 45, Exps. 50-57). Granted, this is not much enhanced stereochemistry, but it is there. However, the major effect of the addition of LiClO₄ to the reactions was a pronounced rate enhancement. Therefore, a rate study was conducted with and without LiClO₄ on the reaction of Me₂Mg with 4-t-butylcyclohexanone at -78°C (Table 46). It was found that the presence of LiClO₄ increased the rate 5 times over that observed for the reaction without LiClO₄. It can be reasoned as for the CH₃Li reactions that the increased polarization resulting from the complexation of the carbonyl group with LiClO₄ enabled the rate of reaction to increase with a slight increase in enhanced stereoselectivity as well.

Organoaluminum Reactions

Chastrette and Amouroux²² have reported that the addition of salts such as NaF or KF or n-Bu₄NX where X = I, Br, Cl or F slowed down the

reaction of R_3Al compounds with benzaldehyde in the order $I > Br > Cl > F$ and $NaF > KF > n-Bu_4NF$. In no case was the reaction faster in the presence of a salt than in the absence of a salt. They suggested that this result was probably due to the deactivating nature of a newly formed complex (C)



between R_3Al and the salt.^{2 3} As the complex becomes more stable the less reactive it becomes.

With this data as precedence, we decided to study further any change in stereochemistry of the products of reaction of Me_3Al with 4-t-butylcyclohexanone in the presence of various salts in diethyl ether. The results are summarized in Table 47. As in the other addition reactions discussed above, only a slight increase (85% to 88%) in the production of the axial alcohol was observed when the reaction was conducted in the presence of $LiClO_4$.

CHAPTER IV

CONCLUSION

It was reported by earlier workers⁵ in this group that the addition of CH_3Li to 4-t-butylcyclohexanone in the presence of LiClO_4 increased the formation of the axial alcohol from 65 to 92% compared to the reaction in the absence of LiClO_4 . In the present study we conducted a more detailed investigation of this unusual observation by allowing other salts, ketones and organolithium compounds to react under these conditions. It was observed that LiClO_4 had the greatest stereochemical effect on the reaction of RLi compounds with cyclohexanones of all the salts tested. When MeLi was allowed to react with 2-methylcyclohexanone in the presence of LiClO_4 , only a modest increase in the stereoselectivity was observed. But with 3,3,5-trimethylcyclohexanone and norcamphor under the same reaction conditions produced no difference in the stereochemistry at all. When phenyllithium was allowed to react with 4-t-butylcyclohexanone and 2-methylcyclohexanone a slight increase in the formation of the axial or cis-alcohols was observed, but for the t-butyllithium reactions, no difference was observed. The major result for all of these reactions was a dramatic increase in the rate of reaction when the reaction are carried out in the presence of LiClO_4 .

When Me_2Mg was allowed to react with ketones in the presence of an equimolar amount of LiClO_4 , slight increases (usually 4%) in the amount of axial alcohol were produced compared to the reaction without added

LiClO_4 . Again an increase in rate was observed. The increase in rate for both the organolithium and Me_2Mg reactions was attributed to the increased reactivity of the complex formed between the carbonyl oxygen and the lithium cation or in other words, the increased polarization of the carbonyl group.

When Me_3Al was allowed to react with 4-t-butylcyclohexanone in the presence of LiClO_4 , no change in the stereochemistry of the methylated product was observed compared to the reaction without LiClO_4 . The addition of salts slowed down the reaction presumably due to deactivation of Me_3Al as a result of complexation with the salt ($\text{Me}_3\text{Al}-\text{LiClO}_4$).

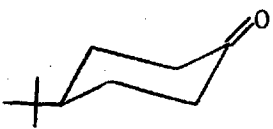
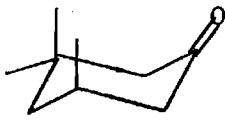

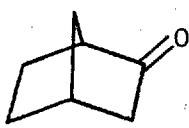
Table 38. Reactions of CH_3Li -Metal Salts with 4- t -Butylcyclohexanone in Diethyl Ether Solvent for 2 Hours at -78°C in 2:1:1 Ratio.

EXP.	SALT	AXIAL ALCOHOL (%) ^a	EQUATORIAL ALCOHOL (%) ^a	% YIELD ^b
1	None	65	35	97
2	NaBPh_4	68	32	97
3	$\text{Al}(\text{NPr}^i)_3$	64	36	80
4	$\text{Al}(\text{OPr}^i)_3$	64	36	85
5	$\text{Mg}(\text{OCH}_3)_2$	68	32	83
6	$\text{Mg}(\text{OPr}^i)_2$	69	31	85
7	Me_4NI	70	30	92
8	LiBr	76	24	99
9	LiI	81	19	98
10	LiOBu^t	75	25	73
11	LiClO_4	92	8	96

a) Normalized % Axial alcohol + % equatorial alcohol = 100%.

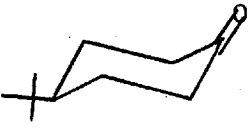

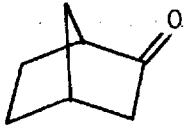
b) Yield was determined by glc and based on an internal standard. No ketone was recovered in any of the experiments.

Table 39. Reactions of $\text{CH}_3\text{Li-LiClO}_4$ with Various Ketones in Et_2O Solvent for 2 Hours at -78°C .

EXP.	KETONE	$\frac{\text{LiClO}_4}{\text{KETONE}}$	AXIAL ALCOHOL (%) ^a	EQUATORIAL ALCOHOL (%) ^a
12		0	65	35
13		1	92	8
14		0	100	0
15		1	100	0
16		0	88	12
17		1	98	4
18		0	100	0
19		1	100	0

a) Normalized % axial alcohol + % equatorial alcohol = 100%. No ketone was recovered in any of the experiments.

Table 40. Rate of Reaction of Ketones with $\text{CH}_3\text{Li-LiClO}_4$ at -78°C in Diethyl Ether Solvent.^a

EXP.	KETONE	TIME	RECOVERED KETONE (%)	AXIAL ALCOHOL (%) ^a	EQUATORIAL ALCOHOL (%) ^a
20	 No LiClO_4	1 min 3 min 5 min 15 min 30 min 60 min	56 45 36 15 6 0	65 65 65 65 65 65	35 35 35 35 35 35
21	With LiClO_4	5 sec 10 sec	0 0	92 92	8 8
22	 No LiClO_4	1 min 3 min 5 min 15 min 30 min 60 min	60 40 33 20 7 0	87 88 88 87 88 88	13 12 12 13 12 12
23	With LiClO_4	5 sec 10 sec	5 0	95 96	5 4
24	 No LiClO_4	1 min 5 min 15 min 30 min 60 min 120 min	70 55 31 15 3 0	100 100 100 100 100 100	0 0 0 0 0 0
25	With LiClO_4	5 sec 10 sec	5 0	100 100	0 0

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

Table 41. Reactions of RLi-LiClO₄ with 4-t-Butylcyclohexanone in Et₂O
Solvent for 2 Hours at -78°C.

EXP.	REAGENT	LiClO ₄ KETONE	RECOVERED KETONE (%)	ADDITION PRODUCTS		REDUCTION
				AXIAL ALCOHOL (%)	EQUATORIAL ALCOHOL (%)	EQUATORIAL ALCOHOL (%)
26	MeLi	0	0	65	35	--
27		1	0	92	8	--
28	<u>t</u> -BuLi	0	30	100	0	7
29		1	37	100	0	<1
30	PhLi	0	0	58	42	--
31		1	0	69	31	--

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

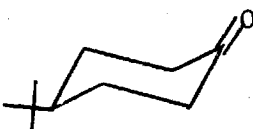

Table 42. Reactions of RLi-LiClO₄ with 2-Methylcyclohexanone in Et₂O Solvent for 2 Hours at -78°C.

EXP.	REAGENT	$\frac{\text{LiClO}_4}{\text{KETONE}}$	RECOVERED KETONE (%)	AXIAL ^a ALCOHOL (%)	EQUATORIAL ^a ALCOHOL (%)
32	MeLi	0	0	88	12
33		1	0	96	4
34	<u>t</u> -BuLi ^b	0	13	100	0
35		1	14	100	00
36	PhLi	0	0	88	12
37		1	0	94	6

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

b) Without LiClO₄ 1% of trans-2-methylcyclohexanol was detected by glc.
With LiClO₄ only a trace of trans-2-methylcyclohexanol was detected by glc.

Table 43. Reactions of *t*-Butyllithium with Ketones in the Presence and Absence of LiClO_4 at -78°C in Et_2O Solvent in 2:1:1 Ratio.

EXP.	KETONE	TIME	RECOVERED KETONE (%)	AXIAL ALCOHOL (%) ^a	EQUATORIAL ALCOHOL (%) ^a
38	 No LiClO_4	5 min	45	100	0
		10 min	35	100	0
		15 min	30	100	0
		30 min	30	100	0
		60 min	30	100	0
		120 min	30	100	0
39	With LiClO_4	5 sec	37	100	0
		10 sec	37	100	0
		60 sec	37	100	0
		120 sec	37	100	0
40	 No LiClO_4	2 min	50	100	0
		5 min	35	100	0
		10 min	26	100	0
		15 min	13	100	0
		30 min	14	100	0
		60 min	13	100	0
		120 min	14	100	0
41	With LiClO_4	5 sec	13	100	0
		10 sec	13	100	0
		60 sec	13	100	0
		120 sec	13	100	0

a) Normalized % axial alcohol + % equatorial alcohol = 100%.


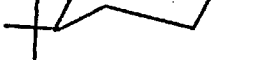
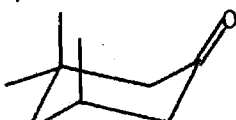
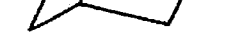


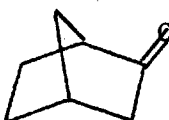

Table 44. Reactions of Me_2Mg -Salt with 4-t-Butylcyclohexanone in Et_2O Solvent for 2 Hours at -78°C in 2:1:1 Ratio.

EXP.	SALT	AXIAL ALCOHOL (%) ^a	EQUATORIAL ALCOHOL (%) ^a	% YIELD ^b
42	None	62	38	96
43	LiClO_4	65	35	96
44	NaBPh_4	60	40	97
45	LiBr	65	35	95
46	LiI	65	35	94
47	LiOBu^t	65	35	70
48	$\text{Mg}(\text{OPr}^i)_2$	74	26	89
49	MeMgOPr^i (only)	75	25	91

a) Normalized % axial alcohol + % equatorial = 100%.

b) Yield was determined by glc using an internal standard. No ketone was recovered in any experiment.

Table 45. Reactions of $\text{Me}_2\text{Mg-LiClO}_4$ with Ketones in Et_2O Solvent for 2 Hours at -78°C in 2:1:1 Ratio.

EXP.	KETONE	$\frac{\text{LiClO}_4}{\text{KETONE}}$	RECOVERED KETONE (%)	AXIAL ALCOHOL (%) ^a	EQUATORIAL ALCOHOL (%) ^a
50		0	0	62	38
51		1	0	62	31
52		0	0	85	15
53		1	0	89	11
54		0	0	80	20
55		1	0	84	16
56		0	0	100	0
57		1	0	100	0

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

Table 46. Reactions of Me_2Mg with 4-*t*-Butylcyclohexanone in the Presence and Absence of LiClO_4 in Et_2O Solvent at -78°C in 2:1:1 Ratio.

EXP.	CONDITIONS		RECOVERED KETONE (%)	AXIAL ALCOHOL (%) ^a	EQUATORIAL ALCOHOL (%) ^a
58	No LiClO ₄	2 min	50	62	38
		5 min	35	62	38
		10 min	20	61	39
		15 min	13	62	38
		30 min	55	63	37
		60 min	0	62	38
		120 min	0	62	38
59	LiClO ₄ Added	10 sec	5	69	31
		20 sec	0	70	30
		40 sec	0	70	30
		60 sec	0	68	32
		120 sec	0	69	31
		120 min	0	69	31

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

Table 47. Reactions of Me_3Al -Salt with 4-t-Butylcyclohexanone in Et_2O Solvent for 12 Hours at -78°C in a 2:1:1 Ratio.

EXP.	SALT	RECOVERED KETONE (%)	AXIAL ALCOHOL (%) ^a	EQUATORIAL ALCOHOL (%) ^a	% YIELD ^b
60	None	0	85	15	98
61	LiClO_4	0	88	12	96
62	NaBPh_4	0	88	12	95
63	LiBr	0	85	15	95
64	LiI	0	85	15	94
65	LiOBu^t	0	85	15	72

a) Normalized % axial alcohol + % equatorial alcohol = 100%.

b) Yield was determined by glc using an internal standard.

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PART V

ALKYLATIONS OF ENONES AND KETONES USING
SUBSTITUTED ALKYLALUMINUM COMPOUNDS

CHAPTER I

INTRODUCTION

Background

It is well known that LiAlH_4 favors 1,2-reduction of enones.¹ On the other hand, the reactivity of LiAlH_4 can be substantially modified by the addition of metal salts. In this connection $\text{LiAlH}_4\text{-AlCl}_3$ has found unusual applicability in epoxide reductions,² $\text{LiAl}(\text{OCH}_3)_3\text{H-CuI}$ can effect reductive removal of halo and mesyloxy groups³ and $\text{LiAlH}_4\text{-TiCl}_3$ has been found to be an excellent coupling reagent.⁴ The $\text{LiAlH}_4\text{-CuI}$ ⁵ reagent has been found to reduce enones conjugatively in 98% yield with 100% regioselectivity. However, it was found that the reactive intermediate was H_2AlI and not CuH or CuAlH_4 .

Recently there has also been an increased interest in methods for effecting 1,4-conjugate addition to α,β -unsaturated systems.⁷ In addition to lithium dialkylcuprate and copper-catalyzed Grignard reagents, Brown and Kabalka⁸ have found that trialkylboranes undergo 1,4-addition to a variety of α,β -unsaturated substrates via a free radical chain process. More recently Kabalka and Daley⁹ found that trialkylaluminum compounds exhibit analogous behavior when photolyzed at -78°C or in the presence of catalytic amounts of oxygen, and were able to demonstrate the intermediacy of free radical species. Ashby and Heinsohn¹⁰ and Mole, *et al.*¹¹ independently have shown that nickel acetylacetonate does catalyze the 1,4-addition of selected enones in high yields and regioselectivity.

Taking into account that the active species in the 1,4-reduction of enones by $\text{LiAlH}_4\text{-CuI}$ is H_2AlI , it seems quite within reason to investigate the possibility of performing the 1,4-addition of enones with substituted alkylaluminum compounds without catalysts.

Purpose

As stated above, earlier workers in this group have shown that H_2AlI provided 100% of the 1,4-conjugate addition product when allowed to react with enones. Therefore we investigated the possibility of using R_2AlX and RAlX_2 compounds to promote the non-catalyzed 1,4-conjugate addition to enones. We also wanted to conduct a systematic study concerning these compounds (e.g. solvents, molar ratios and temperature effects) towards the alkylation of model ketone systems. To achieve these goals we prepared a varied array of substituted alkylaluminum compounds and allowed them to react with representative enones and ketones under consistent conditions.

CHAPTER II

EXPERIMENTAL SECTION

General Considerations

Manipulations of air-sensitive compounds were performed under nitrogen in a glove box equipped with a recirculating system using manganous oxide columns to remove oxygen and dry ice-acetone traps to remove solvent vapors.¹² Reactions were performed under argon or nitrogen at the bench using Schlenk tube techniques.¹³ Syringes equipped with stainless steel needles were used for transfer of reagents. All equipment was flash flamed or heated in an oven and cooled under a flow of nitrogen or argon before use. Proton NMR spectra were obtained at 60 MHz using a Varian A-60 or T-60 NMR spectrometer. GLPC analyses were obtained with a Hitachi (Perkin-Elmer) Model RMU-7 or Varian Model M-66 mass spectrometer. The ir spectra were determined with a Perkin-Elmer, Model 621 or Model 257 infrared recording spectrophotometer.

Analytical

Active CH_3 or C_2H_5 group analysis were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Toepler pump.¹⁶ 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. Halide was determined by titration with AgNO_3 and back titration by KCNS with ferric alum indicator.

Materials

Fisher Reagent Grades anhydrous diethyl ether and tetrahydrofuran (THF) were distilled from LiAlH_4 and NaAlH_4 , respectively prior to use.

Lithium aluminum hydride solutions were prepared by refluxing LiAlH_4 (Alfa Inorganics) in THF or diethyl ether for at least 20 hours followed by filtration through a glass fritted funnel aided by Celite filter aid in the dry box. The clear solution was standardized for aluminum content by EDTA titration.

2,2,6,6-Tetramethyl-trans-4-heptene-3-one, m. p. $43.0-43.7^\circ\text{C}$, NMR: (CCl_4 , TMS), 6.2-7.0 ppm (2 H, quartet, olefinic); 1.10 ppm (18 H, singlet, two t-butyl groups) was obtained from co-workers, J. R. Boone, T. L. Wiesemann and J. J. Lin. Trans-3-penten-2-one, chalcone (Aldrich), 4-t-butylcyclohexanone (Frinton), 2-methylcyclohexanone and 3,3,5-trimethylcyclohexanone (Chemical Samples) were obtained commercially and purified by sublimation or distillation under vacuum.

Diisopropyl amine (Fisher) was purified by distillation over NaOH.

Tert-butyl alcohol (Fisher) was purified by distillation over CaH_2 .

2,2,6,6-Tetramethylcyclohexanol was prepared by the LiAlH_4 reduction at 0°C in diethyl ether of 2,2,6,6-tetramethylcyclohexanone which was prepared by the exhaustive methylation of cyclohexanone in the presence of $\text{NaH-t-BuOH-MeI}^{17}$ (See Part III).

Trimethylaluminum and triethylaluminum were obtained from Texas Alkyls and distilled under vacuum in a dry box. Triphenylaluminum was prepared according to the method of Mole.¹⁴ Aluminum foil (10 g) activated by (aq) HgCl_2 and washed with ethanol and diethyl ether and was stirred under vigorous reflux with diphenylmercury (Alfa Inorganics) (30 g) in

titration. The methyl and ethyl derivatives were also analyzed by normal gas techniques using a standard vacuum line and a Toepler pump.¹⁶

General Reactions of Enones

A 10 X 18 mm test tube equipped with a Teflon coated magnetic stirring bar was dried in a oven or flash flamed and allowed to cool under nitrogen or argon flush and sealed with a rubber serum cap which was connected by means of a syringe needle to a nitrogen-filled manifold and a mineral oil filled bubbler. The alkyl or aryl aluminum reagent (ca. 0.1-0.5 mmole) was syringed into the test tube, and then the calculated amount of enone (in THF or benzene solvent with an internal standard, $n\text{-C}_{12}\text{H}_{26}$ or $n\text{-C}_{14}\text{H}_{30}$) was added to the stirred reagent at the desired temperature. After the designated reaction time, the reaction was quenched slowly with H_2O and dried over MgSO_4 .

Methylation of Enones

The methylation products were determined according to the procedure of Ashby et al¹⁸ A 10 ft. 5% Carbowax 20M on Chromosorb W-NAW column at a flow rate of 55 ml of He/min was used to separate the 1,4- and 1,2-methylation products of 2,2,6,6-tetramethyl-trans-4-hepten-3-one (enone I) (120°C), 3-penten-2-one (enone II) (90°C), chalcone (enone III) (210°C) and 2-cyclohexenone (enone IV) (125°C). Authentic samples of the 1,4- and 1,2-methylation products were obtained from co-workers J. J. Lin and T. L. Wiesemann. The 1,2-methylation products were prepared from the reaction of the enone with CH_3Li , and the 1,4-methylation products were prepared from the reaction of the eneone with $\text{LiCu}(\text{CH}_3)_2$. The per cent yield for each reaction was normalized to 100% = enone recovery % + 1,2-product % + 1,4-product %. Retention times of products varied

slightly depending on glc conditions for enones I and II, but the order of elution was always the same: enone first, 1,4-methylation product second and 1,2-methylation product last. However, when 2-cyclohexenone was the substrate, n-octyl alcohol was employed as the internal standard and the order of retention was 1,2-methylation product first, 1,4-methylation product second and the enone last. The products from the chalcone reaction were determined by ^1H NMR: enone (2 H, vinyl, multiplet at 6.7-7.4 ppm); 1,2-methylation (3 H, methyl group, singlet at 1.43 ppm and 2 H, vinyl, multiplet at 6.5-7.5 ppm); 1,4-methylation (2 H, methylene group, doublet at 2.7 ppm $J = 6 \text{ Hz}$, 3 H, methyl group, doublet at 1.15 ppm $J = 6 \text{ Hz}$ and 1 H, methine, multiplet at 2.80 ppm).

Ethylation of Enones

The ethylation products from the reaction of the $\text{R}_n\text{AlX}_{3-n}$ compounds with 3-penten-2-one (enone II) were determined on a 10 ft. 5% Carbowax 20M on Chromosorb W-NAW column at 130°C with a flow rate of 45 ml of He/min. The order of elution was 1,2-reduction product, enone, 1,4-ethylation product and 1,2-ethylation product. An authentic sample of the 1,2-reduction product, 3-penten-2-ol, was obtained from co-worker J. J. Lin. Pfaltz and Bauer Chemical Company provided an authentic sample of the 1,4-ethylation product, 4-methyl-2-hexanone. The 1,2-ethylation product, 3-methyl-4-hexen-3-ol, was prepared from the reaction of triethylaluminum or ethylmagnesium bromide with the enone.¹⁹

Phenylation of Enones

The phenylation products from the reaction of $\text{Ph}_n\text{AlX}_{3-n}$ compounds with 3-penten-2-one (enone II) were determined on a 10 ft. 5% Carbowax 20M

On Chromosorb W-NAW column at 160°C with a flow rate of 45 ml of He/min. The order of elution was enone first, 1,4-phenylation product and then the 1,2-phenylation product. The 1,2-phenylation product, 2-phenyl-3-penten-2-ol, was obtained from the reaction of phenyllithium with 3-penten-2-one and from the Chemical Samples Company. The 1,4-phenylation product, 4-phenyl-2-pentanone, was isolated by prep glc and analyzed according to the procedure of Melpolder and Heck.²⁶

General Reactions with Ketones

The same general procedure used for the enone reactions described above was followed for the ketone reactions.

Methylation of Ketones

The $\text{Me}_n\text{AlX}_{3-n}$ compounds listed above were allowed to react with 4-t-butylcyclohexanone (ketone I), 3,3,5-trimethylcyclohexanone (ketone II) or 2-methylcyclohexanone (ketone III) in benzene or THF at various temperatures. After the designated reaction time, the reaction with an internal standard, $n\text{-C}_{14}\text{H}_{30}$, was quenched slowly with H_2O and dried over MgSO_4 . A 12 ft. 10% FFAP on Diatoport S column (column temperature: 150°C, helium flow rate: 60 ml/min) was used to separate the products for the 4-t-butylcyclohexanone reaction. The retention time was 13.4 min. for $n\text{-C}_{14}\text{H}_{30}$, 32.7 min. for cis-1-methyl-4-t-butylcyclohexanol, 38.0 min. for 4-t-butylcyclohexanone and 42.0 min. for trans-1-methyl-4-t-butylcyclohexanol. A 12 ft. 10% diglycerol on Diatoport S column at 80°C was used to separate the products from the 2-methylcyclohexanone reaction. The retention time was 4.4 min for the ketone, 5.2 min. for cis-1-methyl-2-methylcyclohexanol, 9.5 min. for trans-1-methyl-2-methylcyclohexanol and 16.0 min. for $n\text{-C}_{14}\text{H}_{30}$. A 10 ft. 20% SAIB on Chromosorb W column at 180°C (flow rate was 60 ml of He/min) was used to determine the products from the

methylation reactions of 3,3,5-trimethylcyclohexanone (ketone III). These conditions gave retention times of 5.0, 4.0 and 6.0 minutes for the ketone, axial alcohol and equatorial alcohol, respectively. Authentic samples of all products were obtained from co-worker J. J. Lin.

Ethylation of Ketones

The ethylation products obtained from the reaction of $\text{Et}_n\text{AlX}_{3-n}$ compounds with 4-t-butylcyclohexanone (ketone I) were determined by a 10 ft. 20% SAIB on Chromosorb W column at 150°C (flow rate of 60 ml of He/min). The retention times for ketone (I), axial alcohol (alkylation), equatorial alcohol (alkylation), axial alcohol (reduction) and equatorial alcohol (reduction) were 30.0, 39.0, 45.0, 28.0 and 32.0 minutes, respectively.

Phenylation of Ketones



The products and their ratios from the reactions of $\text{Ph}_n\text{AlX}_{3-n}$ with 4-t-butylcyclohexanone (ketone I) were determined by the procedure of Ashby, Laemmle and Roling.²¹ After the desired reaction time, the reactions conducted in benzene were subjected to vacuum until all benzene had been removed. Wet diethyl ether was then added to the carbinolate in order to effect hydrolysis. The solution was then transferred to a separatory funnel and the aluminum salts were removed by several washings with distilled water. The ether layer was separated and allowed to evaporate and DMSO-d_6 was added to the sample. The sample was then dried over Linde 4A molecular sieves and transferred to a NMR tube. In those cases where THF or diethyl ether was employed as a solvent, the work-up was identical except that the solution was hydrolyzed directly with distilled water. In the case of the phenylation of 4-t-butylcyclohexanone


(ketone I), the chemical shifts are 4.56 ppm and 4.73 ppm for the axial and equatorial hydroxyl protons, respectively. The assignments of each alcohol hydroxyl peak to a particular isomer were based on numerous reports in the literature concerning their chemical shifts in DMSO and DMSO-d₆.²²

CHAPTER III

RESULTS AND DISCUSSION

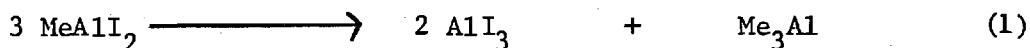
Enone ReactionsMethylation of Enones

Four enones, 2,2,6,6-tetramethyl-trans-4-hepten-3-one (I), 3-penten-2-one (II), chalcone (III) and 2-cyclohexenone (IV), were chosen to react with Me_3Al , Me_2AlCl , Me_2AlBr , Me_2AlI , MeAlI_2 , $\text{Me}_2\text{AlOCH}_3$, $\text{Me}_2\text{AlOBu}^t$, Me_2AlO -, $\text{MeAl}(\text{O}$ -) and $\text{Me}_2\text{AlNPr}_2^1$ in THF and benzene.

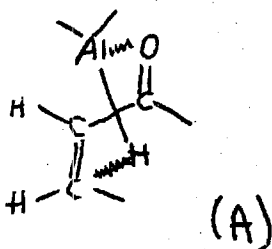
It was expected that for steric reasons the MeAlX_2 compounds would be more regioselective than Me_2AlX or Me_3Al and the regioselectivity of the addition would decrease as the steric requirement of the X group decreases ($\text{I} > \text{Br} > \text{Cl}$ or O - $> \text{OBu}^t > \text{OMe}$).

Earlier workers in this group chose 2,2,6,6-tetramethyl-trans-4-heptene-3-one (enone I) as the representative enone for the regioselective reduction study with $\text{H}_n\text{AlX}_{3-n}$ compounds. Therefore enone (I) was also chosen as the representative enone for this study. The reagents mentioned above were freshly prepared in THF or benzene (Experimental Section) for each reaction and allowed to react with enone (I). The results are shown in Table 48. Very little difference was observed in the results for the reactions in THF or benzene except that in most cases, less starting material was recovered when the reactions were conducted in benzene than in THF. Enone (I) was allowed to react with Me_3Al which resulted in no



1,4-addition at methide:enone = 3. However at methide:enone = 1, small amounts of 1,4-addition (1-5%) were observed. This was expected since the steric requirement of the reagent increases from Me_3Al to Me_2AlOR to MeAl(OR)_2 during the course of the reaction. It is clear from Table 48 that as Cl, Br or I replace a methyl group in the reagent, the amount of recovered enone (I) increases indicating rate retardation because of the increasing steric bulk of the reagents. However, as the rate decreases the amount of 1,4-addition increases in the following order: Me_3Al (1-5%) < Me_2AlCl (5-7%) < Me_2AlBr (20-21%) < Me_2AlI (98-99%) > MeAlI_2 (95%). Therefore we can say that the greater the steric bulk, the slower the reaction but the greater the stereoselectivity of the reagent. However, due to the steric requirement of MeAlI_2 , the addition with enone (I) is much slower compared to Me_2AlI . Because MeAlI_2 reacts so slowly, the regioselectivity suffers slightly probably due to a small amount of AlMe_3 formed by disproportionation (eq. 1).



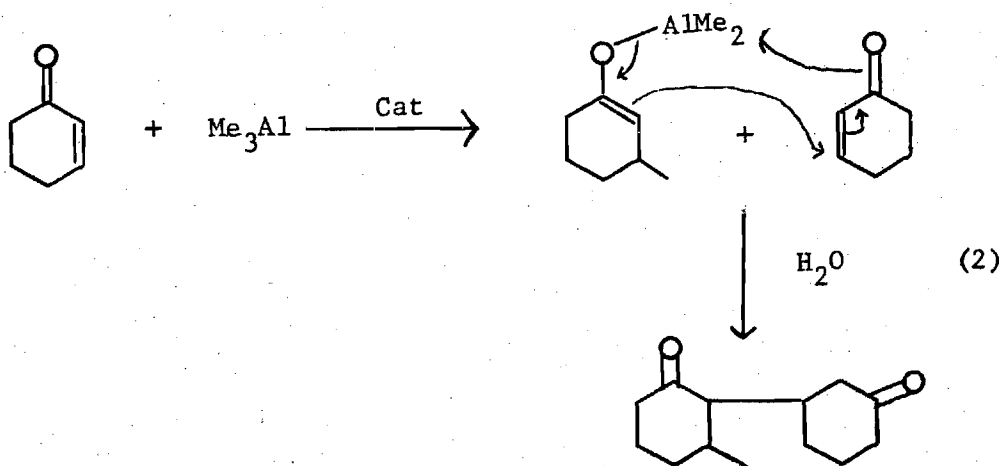
Earlier workers in this group have shown that 1,4 conjugate reduction of enones with H_2AlX compounds resulted from a six-center transition state (A).⁵ This type of transition state would make it more difficult



for the rigid cyclohexenone systems, cis-enones and trans-enones possessing disubstitution at the β -carbon of the enone to accommodate such a transition state (A) and hence these kinds of compounds should react more slowly. Presumably, the 1,4-conjugate addition which took place in the above reactions also proceeded through an analogous transition state and this would explain the rate retardation encountered with bulky reagents or reactants.

When the alkoxy or dialkylamino reagents were allowed to react with enone (I) only starting material was observed with a decrease in mass balance (70-91%). It was expected that Me_2AlO -, $\text{MeAl}(\text{O}$ - $)_2$, $\text{Me}_2\text{AlNPr}_2^1$ and $\text{MeAl}(\text{NPr}_2^1)_2$ which are very bulky reagents would be very selective towards 1,4-addition. However, only starting material (enone I) was observed after being allowed to react with these reagents accompanied by a decrease in mass balance (Table 48).

As Ashby and Heinsohn¹⁰ noted, 1,4-addition can take place forming an intermediate enolate which can then react with starting enone (eq. 2)



when trimethylaluminum is allowed to react with 2-cyclohexenone in the presence of a catalyst (nickel acetylacetonate). A similar sequence is proposed for the $\text{Me}_n\text{AlX}_{3-n}$ reactions which can account for the loss of mass balance.

Since Me_2AlI produced the greatest amount of 1,4-addition product when allowed to react with enone (I), it was decided to allow Me_2AlI to react with other enones, e.g. 3-pentene-2-one (II), chalcone (III) and 2-cyclohexenone (IV) (Table 49). With enone (II), a 55:45 ratio of 1,4:1,2 addition products in THF and a 61:39 ratio in benzene were obtained. Similar results were observed for enones (III) (67:33) and (IV) (65:35); however, for enone (IV) a larger amount of enone was not accounted for presumably due to further reaction of the intermediate enolate as discussed above.

Since the bulky reagents, e.g. $\text{MeAl}(\text{O}-\text{C}_6\text{H}_4)_2$, were not effective for 1,4 conjugate addition to enones, we decided to add bulky coordinating agents, e.g. Ph_3P , $n\text{-Bu}_3\text{P}$ or HMPA to Me_3Al and then allow the mixture to react with enones (I) and (II) (Table 50). It was found that enone (I) reacted very slowly in THF for all of the reactions. In benzene, however Ph_3P allowed only 64% of enone (I) to produce the methylated products with 8% being of the 1,4 orientation, while $n\text{-Bu}_3\text{P}$ allowed only 6% of the enone to react producing a 15:85 ratio of 1,4:1,2 products. No methylated products were observed when HMPA was present.

For enone (II), the addition of coordinating agents listed above increased enolization such that in no case was more than 4% of enone (II) recovered. But with HMPA in THF and benzene, the 1,2-methylation product was obtained in 32 and 47% yields, respectively.

These results do not offer much encouragement for the development of stereoselective reagents towards the methylation of enones.


Ethylation of Enones

To continue our study of non-catalyzed 1,4-addition of organo-aluminum compounds, we allowed a more bulky alkyl group, ethyl, to be present on the aluminum atom. Hence, we allowed $\text{Et AlX}_n\text{X}_{3-n}$ compounds to react with an unencumbered enone, 3-penten-2-one (enone II), in THF or benzene at different times, temperatures and mole ratios of reagent to enone. The results of this study are listed in Table 51.

When Et_3Al was allowed to react with enone (II), the 1,2-ethylation product, 3-methyl-4-hexen-3-ol, was the major product with a small amount (~2%) of the 1,2-reduction product, 3-penten-2-ol, also being produced. As one of the ethyl groups was replaced with Cl, Br or I, the amount of 1,2-reduction product also increased from approximately 3 to 6 to 13%, respectively, in both THF and benzene. However, it should be noted that the benzene reactions always produced less ethylation and more reduction product than the THF reactions. Also, the amount of 1,4-ethylation product also increased from approximately 1 to 3 to 18% as one of the ethyl groups was replaced with Cl, Br or I, respectively. If two iodo groups were introduced into the system, the amount of 1,4-ethylation increased to ~28%, but the 1,2-reduction product also increased to 35%. These results are reminiscent of the $\text{Me AlX}_n\text{X}_{3-n}$ reactions discussed above.

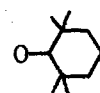
An observation for this reaction which differed from the $\text{Me AlX}_n\text{X}_{3-n}$ reactions was that in no case was starting enone recovered. However, the mass balances were approximately the same which implies that the alkylation reactions take place at about the same rate for both systems, but the β -

reduction pathway in the $\text{Et}_n\text{AlX}_{3-n}$ system is prominent because of the increased steric requirements.

If more bulky groups (e.g. NPr_2^i , OBu^t , or O -) were introduced into the system, the amount of 1,4-addition or 1,2-reduction was not increased, but the mass balance was lowered considerably (32-42%) which was also observed for the $\text{Me}_n\text{AlX}_{3-n}$ reactions. This result may also be attributed to the already discussed enolization reactions.

Phenylation of Enones

When triphenylaluminum, a bulky reagent, was allowed to react with an unencumbered enone such as 3-penten-2-one (II) (Table 52), 60% of the 1,4-phenylation product was observed via glc. As other $\text{Ph}_n\text{AlX}_{3-n}$ compounds were allowed to react with enone (II), an increase in the production of 1,4-addition product was observed for $\text{X} = \text{Cl}$ (65%), Br (90%) and I (100%) but accompanied by a lower mass balance (approximately 77, 75 and 66% in both THF and benzene). This may be explained on the basis that as the amount of 1,4-addition increases, the newly formed enolate can attack starting enone (eq. 2). This explanation accounts for the observation of no recovered enone and is confirmed by the fact that when PhAlI_2 was allowed to react with enone (II) 100% of the 1,4-addition product was produced but only in ~10% yield. The two large iodine atoms slow down the reaction considerably, and, therefore, the newly formed enolate has plenty of time to react with starting enone and thereby lower the yield of 1,4-addition product.

If other bulky substituents (e.g. NPr_2^i , OBu^t , and O -) were introduced into the system, 74, 76 and 81% of the 1,4-addition product was



observed, respectively. However, just as for the other reactions described above, only a small yield (approximately 25, 22 and 11%, respectively) of the phenylated product was obtained with no starting enone recovered. Direct enolization or the reaction of the newly formed 1,4-enolate with starting enone may be responsible for this low mass balance.

Ketone Reactions

Methylation of Ketones

A most unusual observation was made when it was found that Me_3Al attack is favored by $\sim 85\%$.^{24,25} It was shown that in hydrocarbon solvent "compression effects" controlled the product distribution when reagent to ketone ratios were 2:1 or greater.²¹ In ratios less than 2:1 or in THF, steric effects were the effective force. Therefore, $\text{Me}_n\text{AlX}_{3-n}$ compounds were allowed to react with ketones with bulky substituents in order to observe their effectiveness towards stereoselective addition.

The following reagents were allowed to react with a compounds were allowed to react with a representative ketone, 4-t-butylcyclohexanone, in order to observe their effectiveness towards stereoselective addition.

The following reagents were investigated in THF and benzene at different times, temperatures and mole ratios of reagent to ketone: Me_3Al , Me_2AlCl , Me_2AlBr , Me_2AlI , MeAlI_2 , $\text{Me}_2\text{AlNPr}_2^1$, $\text{Me}_2\text{AlOCH}_3$, $\text{Me}_2\text{AlOBu}^t$, Me_2AlO -, and $\text{MeAl}(\text{O}$ - $)_2$. The results of this study are listed in Table 53. It was found that increasing the steric bulk of the methylaluminum halide reagents from Cl to Br to I had little effect on the stereoselectivity of the reaction. However, the increased steric bulk of the


reagent decreased the rate of reaction and therefore, 80, 83 and 97% of the ketone was recovered according to glc analysis.

However in benzene, a reagent/ketone ratio of 3:1 also had little effect on the stereoselectivity (6-10% axial alcohol), but as the halo substituents changed from Cl to Br to I the yield of addition product decreased from 95% for Me_3Al to 79% to 66% to 53%, respectively which reflects the increased steric bulk of the reagents. Also, the amount of recovered ketone increased from 0% to 17% to 25% to 40% respectively. This also reflects the increased steric bulk by decreasing the rate of reaction.

At a reagent/ketone ratio of 1:1 in benzene the increase in the bulkiness of the halo substituent decreased the rate of reaction as was indicated by the amount of recovered ketone (e.g. Me_3Al (33%), Me_2AlCl (70%), Me_2AlBr (80%) and Me_2AlI (87%)). Also, the amount of axial alcohol decreased from Me_3Al (75%), to Me_2AlCl (57%) to Me_2AlBr (40%) to Me_2AlI (20%). Therefore, it may be assumed, that the increased bulkiness of the reagent does indeed increase the stereoselectivity of the reagent.

If two iodo groups are introduced into the reagent, MeAlI_2 , the rate is slowed down even more in both THF and benzene resulting in 97% recovery of ketone (I) in THF, 91% recovery in benzene when the reagent/ketone ratio was 1:1 and 50% when the ratio was 3:1, results which compare to 40% obtained for Me_2AlI under the same conditions. The production of axial alcohol remained around 6% in a 3:1 ratio of reagent to ketone in benzene, but in a 1:1 ratio the axial alcohol decreased to 18% which was only a 2% decrease from that observed for the Me_2AlI reaction. Therefore, it may be safe to assume that Me_2AlI is the most stereoselective reagent studied,

but with only 6% of the ketone methylated it is not a practical reagent.

If other bulky groups (ca. NPr_2^i , OCH_3 , OBu^t ,  or $(\text{O}-\text{C}_6\text{H}_{10})_2$) were introduced into the reagent, the major product obtained from the reaction of these reagents with ketone (I) was recovered ketone. Therefore it may be assumed that the reaction was very slow or enolization took place as was indicated by a very low mass balance for the $\text{MeAl}(\text{O}-\text{C}_6\text{H}_{10})_2$ reaction (0-8%). The amount of addition product ranged from 0% to 20%. In all cases the major alcohol product was the axial alcohol (80-100%).

The above reagents represented attempts to influence the distribution of products by steric bulk of the reagents. It was also of importance to observe the effect when strong bulky coordinating solvents, e.g. Ph_3P , $n\text{-Bu}_3\text{P}$, HMPA or DME, were introduced with the ketone and then allowed to react with trimethylaluminum (Table 54). No significant change in stereochemistry from that of Me_3Al alone was observed, however enolization increased and the reaction slowed down considerably as indicated by a large amount of recovered ketone.

Ethylation of Ketones

To continue our study of ketone addition reactions, we allowed a representative ketone, 4-t-butylcyclohexanone, (Table 55) to react with $\text{Et}_n\text{AlX}_{3-n}$ compounds where $\text{X} = \text{Cl}, \text{Br}$ or I . The amino- and alkoxy-reagents were not prepared since enolization was the main reaction for the $\text{Me}_n\text{AlX}_{3-n}$ compounds. Also, since the stereochemistry of the alcohol products from the same reactions in THF remained almost the same throughout the study, the $\text{Et}_n\text{AlX}_{3-n}$ compounds were decided to be carried out in benzene only.

For the reaction of Et_3Al with ketone (I) in a 1:1 ratio, 46% of ketone (I) was recovered, but 50% of the ketone was either ethylated (64%)

or reduced (36%). Of the ethylated products, 79% was the axial alcohol while 81% of the reduced product was the equatorial alcohol. As one Cl, or Br or I group was introduced in the reagent under these conditions, the amount of recovered ketone remained essentially the same ($\sim 30\%$). This was a decrease of roughly 16% from the Et_3Al reaction. Also, the amount of ethylated product decreased to 41, 40 and 43%, respectively, compared to 64% from the Et_3Al reaction. Therefore, one can conclude that with the introduction of halogens, the β -reduction pathway becomes prominent. Also, for the ethylated product, there was an initial decrease in the percent of axial alcohol produced from the Et_3Al reaction compared to Et_2AlCl . But, then there was a steady increase in the axial alcohol from Cl to Br to I (65 to 70 to 75%, respectively). However, the percent of the reduced axial alcohol remained constant at 20%. This reflects the increasing steric bulk of the reagents.

For the 3:1 ratio of reagent to ketone reactions, $\sim 6\%$ of the ketone was recovered for the Et_2AlX reactions compared to no recovered ketone for Et_3Al . The amount of ethylated and reduced products (40-43% and 57-60% respectively) remained constant throughout the halide series. but the amount of axial ethylated alcohol decreased from Cl(27%) to Br(20%) to I(15%), again reflecting the increasing steric bulk of the reagent. The reduced axial alcohol remained constant for the chloride (26%) and bromide (25%) reactions but increased for the iodide reaction (35%).

The trends observed for the mono halide reactions were amplified for the EtAlI_2 reactions because of the greatly increased steric bulk of the reagent. That is, a larger amount of ketone was recovered for both

the 1:1 ratio and 3:1 ratio of reagent to ketone reactions (60 and 49% respectively). Also, for the 1:1 ratio reaction, a larger amount of the ethylated axial alcohol (80%) and reduced axial alcohol (17%) were observed although the amount of ethylated and reduced alcohols remained the same (25 and 75% respectively) as those observed for the Et_2AlX reactions. A major difference in the ratio of products occurred for the reaction in which the reagent to ketone ratio was 3:1. In this case, 91% of the reacted ketone was converted to the reduced alcohol with 32% of that a result which was greater than twice that observed for the Et_2AlI reaction. Hence EtAlI_2 is the most stereoselective; however, with such a low yield of alcohols, it is an impractical reagent.

Phenylation of Ketones

The phenylanalogs of the above reagents were prepared according to the procedure described in the Experimental Section. They were all allowed to react with ketone (I) in benzene at different mole ratios with the results listed in Table 56. Because the above reactions showed no enhanced stereoselectivity in THF, only benzene reactions were carried out. The 3:1 reagent to ketone ratio reactions showed no enhanced stereoselectivity just as for the methylation or ethylation reactions described above (92-95% equatorial alcohol). The most interesting reactions were those where the reagent to ketone ratio was 1:1. As the group size increased from Cl to Br to I, the amount of recovered ketone (50 to 55 to 65%, respectively) and equatorial alcohol (60 to 63 to 70%, respectively) also increased. Also, PhAlI_2 , when allowed to react with ketone (I), continued the trend with 80% recovered ketone but the percent of phenylated equatorial alcohol increased to 75% compared to 25% for the axial alcohol.

This once again points out the fact that as the reagent becomes larger the stereoselectivity also increased but the yield is so low that the reagent is impractical.

CHAPTER IV

CONCLUSION

The major conclusion from this study is that the greater the steric bulk of the R_nAlX_{3-n} compounds the greater the stereoselectivity, with the best reagent being R_2AlI . But, because of low yields, the use of substituted organoaluminum reagents is impractical for the addition to enones and/or ketones.

Table 48. Reactions of $\text{Me}_n\text{AlX}_{3-n}$ Compounds With Enone (I).

REAGENT	REAGENT	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED ENONE (%) ^b	ALKYLATION PRODUCTS (%) ^a		
	ENONE					TOTAL	1,4	1,2
Me ₃ Al	1	THF	RT	24	20	75	3	97
	3				20	76	1	99
	1				17	78	3	97
	3				16	77	2	98
	1	Benzene	RT	24	2	97	5	95
	3				1	96	1	99
	1				2	94	4	96
	3				2	93	1	99
Me ₂ AlCl	1	THF	RT	24	25	71	6	94
	3				24	70	5	95
	1	Benzene			21	70	7	93
	3				20	70	6	94

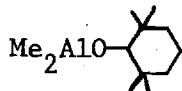
Table 48 (Continued)

REAGENT	REAGENT ENONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED ENONE (%) ^b	ALKYLATION PRODUCTS (%) ^a		
						TOTAL	1,4	1,2
Me_2AlBr	1	THF	RT	24	35	58	20	80
	3				33	58	20	80
	1	Benzene			32	57	20	80
	3				31	58	21	79
Me_2AlI	1	THF	RT	24	53	42	98	2
	3				50	42	98	2
	1	Benzene	RT	24	47	47	99	1
	3				46	47	99	1
MeAlI_2	1	THF	RT	24	61	32	100	0
	3				60	32	100	0
	1	Benzene	RT	24	55	39	100	0
	3				54	39	100	0

Table 48 (Continued)

REAGENT	REAGENT	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED ENONE (%) ^b	ALKYLATION PRODUCTS (%) ^a		
	ENONE					TOTAL	1,4	1,2
$\text{Me}_2\text{Al}(\text{NPr})_2^{\text{i}}$	1	THF	RT	24	89	0	0	0
	3				87	0	0	0
	1	Benzene	RT	24	76	0	0	0
	3				75	0	0	0
$\text{Me}_2\text{AlOCH}_3$	1	THF	RT	24	75	0	0	0
	3				75	0	0	0
	1	Benzene	RT	24	70	0	0	0
	3				65	0	0	0
$\text{Me}_2\text{AlOBu}^{\text{t}}$	1	THF	RT	24	91	0	0	0
	3				91	0	0	0
	1	Benzene	RT	24	72	0	0	0
	3				70	0	0	0

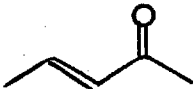
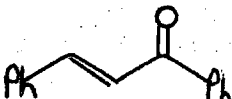
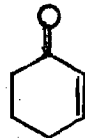
Table 48 (Continued)

REAGENT	REAGENT	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED ENONE (%) ^b	ALKYLATION PRODUCTS (%) ^a		
	ENONE					TOTAL	1,4	1,2
	1	THF	RT	24	91	0	0	0
	3				91	0	0	0
	1	Benzene			89	0	0	0
	3				89	0	0	0

a) Normalized as per cent 1,4-product + per cent 1,2-product = 100%.

b) Yield determined by glc and based on internal standard.

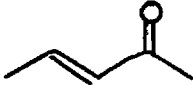
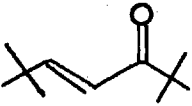
Table 49. Reactions of Me_2AlI With Other Enones in Benzene and THF at Room Temperature for 24 Hours in a 2:1 Ratio.

ENONE	SOLVENT	RECOVERED ENONE (%) ^a	METHYLATION PRODUCTS (%) ^b		
			TOTAL	1,4	1,2
	THF	39	40	55	45
	Benzene	20	39	61	39
	THF	33	60	67	33
	Benzene	15	75	68	32
	THF	50	40	65	25
	Benzene	45	38	66	24

a) Yield determined by glc and based on an internal standard.

b) Normalized as % 1,4-product + % 1,2-product = 100%.

Table 50. Reactions of Me_3Al With Enone (I) and Enone (II) in the Presence of Coordinating Agents at Room Temperature for 24 Hours.

ENONE	COORDINATING AGENT	SOLVENT	RECOVERED ENONE (%) ^a	METHYLATION PRODUCTS (%) ^b		
				TOTAL	1,4	1,2
	Ph_3P	THF	0	0	0	0
		Benzene	0	0	0	0
	$\text{n-Bu}_3\text{P}$	THF	0	0	0	0
		Benzene	4	0	0	0
	HMPA	THF	0	32	0	100
		Benzene	0	47	0	100
	Ph_3P	THF	91	0	0	0
		Benzene	28	64	8	92
	$\text{n-Bu}_3\text{P}$	THF	90	2	0	100
		Benzene	89	6	15	85
	HMPA	THF	90	0	0	0
		Benzene	89	0	0	0

a) Yield determined by glc and based on an internal standard.

b) Normalized as % 1,4-product + % 1,2-product = 100%.


Table 51. Reactions of $\text{Et}_n\text{AlX}_{3-n}$ Compounds With Enone (II).

REAGENT	REAGENT ENONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED ENONE (%) ^c	ADDITION PRODUCTS (%)			REDUCTION PRODUCTS (%)		
						TOTAL ^a	1,4 ^b	1,2 ^b	TOTAL ^a	1,4 ^b	1,2 ^b
Et_3Al	1	THF	RT	24	0	93	Trace	100	1	0	100
	3				0	92	Trace	100	1	0	100
	1		45	8	0	90	Trace	100	1	0	100
	3				0	90	Trace	100	1	0	100
	1	Benzene	RT	24	0	92	Trace	100	1	0	100
	3				0	93	Trace	100	1	0	100
	1		45	8	0	90	Trace	100	1	0	100
	3				0	91	Trace	100	1	0	100
Et_2AlCl	1	THF	RT	24	0	90	Trace	100	3	0	100
	3				0	90	Trace	100	2	0	100
	1	Benzene	RT	24	0	85	1	99	4	0	100
	3				0	84	1	99	3	0	100
Et_2AlBr	1	THF	RT	24	0	85	1	99	5	0	100
	3				0	84	1	99	5	0	100
	1	Benzene	RT	24	0	78	3	97	6	0	100
	3				0	75	4	96	6	0	100

Table 51 (Continued)

REAGENT	REAGENT ENONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED ENONE (%) ^c	ADDITION PRODUCTS (%)			REDUCTION PRODUCTS (%)		
						TOTAL ^a	1,4 ^b	1,2 ^b	TOTAL ^a	1,4 ^b	1,2 ^b
Et ₂ AlI	1	THF	RT	24	0	80	15	85	12	0	100
	3				0	79	17	83	13	0	100
	1	Benzene	RT	24	0	75	18	82	13	0	100
	3				0	73	19	81	14	0	100
EtAlI ₂	1	THF	RT	24	0	50	27	73	30	0	100
	3				0	49	28	72	31	0	100
	1	Benzene	RT	24	Trace	45	28	72	35	0	100
	3				Trace	46	29	71	36	0	100
Et ₂ AlNPr ¹ ₂	1	THF	RT	24	0	35	15	85	10	0	100
	3				0	34	16	84	11	0	100
	1	Benzene	RT	24	0	31	16	84	11	0	100
	3				0	31	15	85	11	0	100

Table 51 (Continued)

REAGENT	REAGENT ENONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED ENONE (%) ^c	ADDITION PRODUCTS (%)			REDUCTION PRODUCTS (%)		
						TOTAL ^a	1,4 ^b	1,2 ^b	TOTAL ^a	1,4 ^b	1,2 ^b
Et ₂ AlO- 	1	THF	RT	24	0	30	13	87	7	0	100
	3				0	29	13	87	7	0	100
	1	Benzene	RT	24	0	25	14	86	8	0	100
	3				0	25	15	85	7	0	100

a) Normalized as % addition products + reduction products = 100%.

b) Normalized as % 1,4-product + % 1,2-product = 100%.

c) Normalized as % total products + % enone = 100%.

Table 52. Reactions of $\text{Ph}_n\text{AlX}_{3-n}$ Compounds With Enone (II).

REAGENT	REAGENT ENONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED ENONE (%) ^a	ADDITION PRODUCTS (%) ^b		
						TOTAL	1,4	1,2
Ph_3Al	1	THF	RT	24	0	80	60	40
	3				0	79	60	40
	1		45	8	0	79	61	39
	3				0	80	61	39
	1	Benzene	RT	24	0	80	60	40
	3				0	81	59	41
	1		45	8	0	79	59	41
	3				0	78	59	41
Ph_2AlCl	1	THF	RT	24	0	78	64	36
	3				0	78	65	35
	1	Benzene	RT	24	0	77	65	35
	3				0	75	65	35

Table 52 (Continued)

REAGENT	REAGENT ENONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED ENONE (%) ^a	ADDITION PRODUCTS (%) ^b		
						TOTAL	1,4	1,2
Ph_2AlBr	1	THF	RT	24	0	75	88	12
	3				0	75	89	11
	1	Benzene	RT	24	0	74	89	11
	3				0	73	90	10
Ph_2AlI	1	THF	RT	24	0	64	100	0
	3				0	66	100	0
	1	Benzene	RT	24	0	66	100	0
	3				0	65	100	0
PhAlI_2	1	THF	RT	24	0	45	100	0
	3				0	44	100	0
	1	Benzene	RT	24	0	40	100	0
	3				0	39	100	0

Table 52 (Continued)

REAGENT	REAGENT ENONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED ENONE (%) ^a	ADDITION PRODUCTS (%) ^b		
						TOTAL	1,4	1,2
$\text{Ph}_2\text{AlNPr}_2^{\text{i}}$	1	THF	RT	24	70	25	74	26
	3				68	25	74	26
	1	Benzene	RT	24	65	27	75	25
	3				66	26	74	26
$\text{Ph}_2\text{AlOCH}_3$	1	THF	RT	24	70	25	75	25
	3				72	26	74	26
	1	Benzene	RT	24	65	25	75	25
	3				65	25	75	25
$\text{Ph}_2\text{AlOBu}^{\text{t}}$	1	THF	RT	24	75	22	76	24
	3				73	22	76	24
	1	Benzene	RT	24	75	22	76	24
	3				75	22	76	24

Table 52 (Continued)

REAGENT	REAGENT ENONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED ENONE (%) ^a	ADDITION PRODUCTS (%) ^b		
						TOTAL	1,4	1,2
$\text{Ph}_2\text{Al}(\text{O}-\text{C}_6\text{H}_2\text{Me}_2)$	1	THF	RT	24	90	11	81	19
	3				90	11	81	19
	1	Benzene	RT	24	89	10	80	20
	3				90	11	80	20

a) Yield determined by glc and based on an internal standard.

b) Normalized as % 1,4-product + % 1,2-product = 100%.

Table 53. Reactions of $\text{Me}_n\text{AlX}_{3-n}$ Compounds With 4-t-Butylcyclohexanone, Ketone (I).

REAGENT	REAGENT KETONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED KETONE (%) ^a	ADDITION PRODUCTS (%) ^b		
						TOTAL	AXIAL ALCOHOL	EQUATORIAL ALCOHOL
Me_3Al	1	THF	RT	24	50	47	85	15
	3				50	48	86	14
	1		45	8	45	45	85	15
	3				40	50	83	17
	1	Benzene	RT	24	50	45	76	24
	3				1	97	11	89
	1		45	8	33	59	75	25
	3				0	95	9	91
Me_2AlCl	1	THF	RT	24	80	17	85	15
	3				80	18	83	17
	1	Benzene	RT	24	70	26	57	43
	3				17	79	10	90

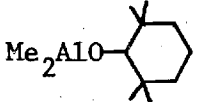
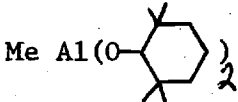
Table 53 (Continued)

REAGENT	REAGENT KETONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED KETONE (%) ^a	ADDITION PRODUCTS (%) ^b		
						TOTAL	AXIAL ALCOHOL	EQUATORIAL ALCOHOL
Me ₂ AlBr	1	THF	RT	24	83	15	80	20
	3				83	16	80	20
	1	Benzene	RT	24	80	12	40	60
	3				25	66	8	92
Me ₂ AlI	1	THF	RT	24	93	7	79	21
	3				90	7	79	21
	1	Benzene	RT	24	87	6	20	80
	3				40	53	7	93
MeAlI ₂	1	THF	RT	24	97	1	80	20
	3				97	1	80	20
	1	Benzene	RT	24	91	4	18	72
	3				50	46	6	94

Table 53 (Continued)

REAGENT	REAGENT KETONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED KETONE (%) ^a	ADDITION PRODUCTS (%) ^b		
						TOTAL	AXIAL ALCOHOL	EQUATORIAL ALCOHOL
$\text{Me}_2\text{AlNPr}_2^i$	1	THF	RT	24	60	20	85	15
	3				55	20	85	15
	1	Benzene	RT	24	55	1	100	0
	3				47	1	100	0
$\text{Me}_2\text{AlOCH}_3$	1	THF	RT	24	80	5	85	15
	3				70	10	86	14
	1	Benzene	RT	24	75	5	86	14
	3				68	11	85	15
$\text{Me}_2\text{AlOBu}^t$	1	THF	RT	24	61	5	80	20
	3				59	5	80	20
	1	Benzene	RT	24	60	5	85	15
	3				58	8	86	14

Table 53 (Continued)

REAGENT	REAGENT KETONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED KETONE (%) ^a	ADDITION PRODUCTS (%) ^b		
						TOTAL	AXIAL ALCOHOL	EQUATORIAL ALCOHOL
	1	THF	RT	24	55	1	100	0
	3				50	1	100	0
	1	Benzene	RT	24	50	4	100	0
	3				40	0	0	0
	1	THF	RT	24	7	1	100	0
	3				2	1	100	0
	1	Benzene	RT	24	5	1	100	0
	3				0	0	0	0

a) Yield was determined by glc and based on an internal standard.

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

Table 54. Reactions of Me_3Al With Ketone (I) in the Presence of Coordinating Agents at Room Temperature for 24 Hours in a 1:1:1 Ratio.

COORDINATING AGENT	SOLVENT	RECOVERED KETONE (%) ^a	METHYLATION PRODUCTS (%) ^b		
			TOTAL	AXIAL	EQUATORIAL
Ph_3P	Benzene	70	3	75	25
	THF	75	5	85	15
$\text{n-Bu}_3\text{P}$	Benzene	70	5	75	25
	THF	70	5	75	25
HMPA	Benzene	60	5	75	25
DME	Benzene	55	4	75	25

a) Yield was determined by glc and based on an internal standard.

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

Table 55. Reactions of $\text{Et}_n\text{AlX}_{3-n}$ Compounds With 4-t-Butylcyclohexanone, Ketone (I).

REAGENT	REAGENT KETONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED KETONE (%) ^c	ADDITION PRODUCTS (%)			REDUCTION PRODUCTS (%)		
						TOTAL ^a	AXIAL ALCOHOL ^b	EQUATORIAL ALCOHOL ^b	TOTAL ^a	AXIAL ALCOHOL ^b	EQUATORIAL ALCOHOL ^b
Et_3Al	1	THF	RT	24	35	65	88	12	35	22	78
	3				0	80	88	12	20	22	78
	1	Benzene	RT	24	46	64	79	21	36	19	81
	3				0	72	8	92	28	29	71
Et_2AlCl	1	Benzene	RT	24	31	31	65	35	69	20	80
	3				6	41	27	73	59	26	74
Et_2AlBr	1	Benzene	RT	24	30	29	70	30	71	20	80
	3				6	40	20	80	60	25	75
Et_2AlI	1	Benzene	RT	24	30	27	75	25	73	20	80
	3				5	43	15	85	57	35	65
EtAlI_2	1	Benzene	RT	24	60	25	80	20	75	17	83
	3				49	9	35	65	91	32	68

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

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

c) Normalized as % total alcohol + % ketone = 100%.

Table 56. Reactions of $\text{Ph}_n\text{AlX}_{3-n}$ Compounds With 4-t-Butylcyclohexanone, Ketone (I).

REAGENT	REAGENT KETONE	SOLVENT	TEMP (°C)	TIME (hr)	RECOVERED KETONE (%) ^a	ADDITION PRODUCTS (%) ^b		
						TOTAL	AXIAL ALCOHOL	EQUATORIAL ALCOHOL
Ph_3Al	1	Benzene	RT	24	45	50	51	49
	3				0	95	8	92
Ph_2AlCl	1				50	43	40	60
	3				5	90	5	95
Ph_2AlBr	1				55	40	45	55
	3				15	80	6	94
Ph_2AlI	1				65	30	30	70
	3				25	65	5	95
PhAlI_2	1				80	15	25	75
	3				40	50	5	95

a) Yield was determined by glc and based on an internal standard.

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

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ERRATA

<u>Page</u>	<u>Line</u>	
xviii	14	examine
xix	13 & 15	stereoselective
2	13 & 15	"product
3	7	...and Ashby and colleagues have
55	Table 7	products should be R not H
58	Title	alkenes
117	5	excellent
233	1	It is well known that