ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS

A THESIS

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ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS

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SUMMARY

PART I. THE EVALUATION OF HYDRIDE REAGENTS FOR CONJUGATE REDUCTION OF ENONES

Conjugate reduction of six enones by the new reagent $LiAlH_4$-CuI has been studied. The optimum conditions for conjugate reduction depend on the ratio of $LiAlH_4$:CuI:enone, temperature, solvent, and reaction time involving contact of $LiAlH_4$ and CuI before the enone is added. Enone I (see Table 1) can be reduced in quantitative yield and 100% regioselectivity in 1 hr or less when the ratio of $LiAlH_4$:CuI:enone is 1:4:1, the solvent is THF and the temperature is 0°. Enones II-VI (see Table 1) can also be reduced in high yield and 100% regioselectivity. Reduction of enones I and III with $LiAlH_4$-$TiCl_3$ proceeds with 100% regioselectivity, however the yields are lower (66 and 34%, respectively) compared with the results obtained with the $LiAlH_4$-CuI reagent. The reagent $LiAlH_4$-$FeCl_3$ was found to be ineffective for conjugate reduction. The new reagents, $LiAlH_4$-CuI and $LiAlH_4$-$TiCl_3$, show different stereoselectivity than $LiAlH_4$ toward 4-tert-Butylcyclohexanone and 3,3,5-trimethylcyclohexanone. Compared with $LiAlH_4$-CuI, related reagents ($LiAlH_4$-CuCl, $LiAlH_4$-HgI_2 and $LiAlH_4$-$HgCl_2$) show less regioselectivity in enone reduction, however, the reagent AlH_3-CuI is as effective in conjugate reduction as $LiAlH_4$-CuI. H_2AlI has been found to be the reactive species of the reagents $LiAlH_4$-CuI and AlH_3-CuI. The compounds H_2AlX and $HAlX_2$ where X = I, Br and Cl were synthesized independently

and were evaluated as conjugate reducing agents.

$HAl(O\underline{t}\text{-}Bu)_2$, $HAl(O\underline{i}\text{-}Pr)_2$ and $HAl[N(\underline{i}\text{-}Pr)_2]_2$ have also been found to be effective conjugate reducing agents. The alane, $HAl[N(\underline{i}\text{-}Pr)_2]_2$ in particular produced from the enones studies the 1,4-reduction product in quantitative yield and 99.5% regioselectivity. A six-center transition state for reduction was proposed.

PART II. REACTIONS OF NEW ORGANOCUPRATES

(II-1) Regioselective Methylation of Enones

The new organocuprates, $LiCu_2(CH_3)_3$, $Li_2Cu(CH_3)_3$ and $Li_2Cu_3(CH_3)_5$ were allowed to react with six representative enones in ether and THF in order to evaluate their regioselectivity and reaction rate compared to $LiCu(CH_3)_2$. In general, $LiCu_2(CH_3)_3$ in THF gave 100% regioselectivity in effecting 1,4- addition although its rate of reaction was slightly less than that of $LiCu(CH_3)_2$. On the other hand, $Li_2Cu(CH_3)_3$ reacted more rapidly in ether than did $LiCu(CH_3)_2$ with the same enones; however, when the enones were sterically hindered by α,β or β,β substitution, a significant amount of 1,2-addition product was observed. In THF, $Li_2Cu(CH_3)_3$ behaved very much like $LiCu(CH_3)_2$ except toward β,β-disubstituted enones. In ether, $Li_2Cu_3(CH_3)_5$ gave 100% 1,4-addition in each case studied and reacted more rapidly than $LiCu(CH_3)_2$.

(II-2) Substitution Reactions of Alkyl-, Cycloalkyl- and Aryl Halides

The new cuprates $LiCu_2(CH_3)_3$, $Li_2Cu(CH_3)_3$ and $Li_2Cu_3(CH_3)_5$ in Et_2O and THF have been compared to $LiCu(CH_3)_2$ and CH_3Li in their substitution reaction toward alkyl-, cycloalkyl- and aryl halides (where halogen = I, Br, Cl, F). In most cases the new cuprate

$Li_2Cu(CH_3)_3$ was superior to all other reagents and in some cases the superiority was substantial.

(II-3) Concerning the Reaction of Organocuprates with 4-tert-Butylcyclohexanone

The previously reported unusual stereochemistry in the reaction of 4-*tert*-butylcyclohexanone with $CH_3Li-LiCu(CH_3)_2$ is attributed to complexation of the ketone by $LiCu(CH_3)_2$ followed by addition of CH_3Li to the carbonyl group rather than by addition of a $CH_3Li-LiCu(CH_3)_2$ complex, *e.g.* $Li_2Cu(CH_3)_3$ directly to the uncomplexed ketone.

PART III. APPLICATION OF COMPLEX METAL HYDRIDES OF COPPER IN ORGANIC REACTIONS

A series of stable complex metal hydrides of copper of composition $Li_nCuH_{(n+1)}$ (n=1 to 5), prepared by the reaction of $LiAlH_4$ with the corresponding lithium methylcuprates in diethyl ether, has been allowed to react with selected alkyl halides, enones, and cyclic ketones in both diethyl ether and THF. It has been shown that the different hydrides exhibit different reducing capabilities towards alkyl halides, different regioselectivities towards enones, and different stereoselectivities towards cyclic ketones. These data support the integrity of each hydride as a single compound rather than a physical mixture. Tetrahydrofuran soluble Li_4CuH_5 has been shown to be the most reactive of the complex metal hydrides of copper toward alkyl halides in that this hydride reduced 1-iodo-, 1-bromo-, and 1-chlorodecane in 100, 100 and 99% yields, respectively. The complex metal hydrides of copper reduce enones predominantly 1, 4 (Li_2CuH_3, 96%) or 1, 2 (Li_4CuH_5, 95%)

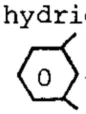
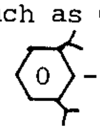
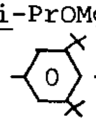
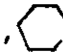
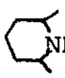
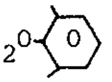
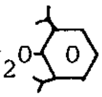
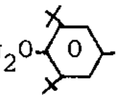
depending on the hydride. In most cases, the complex metal hydrides of copper reduce 4-tert-butylcyclohexanone predominantly from the axial side as in the case of $LiAlH_4$. Other cyclohexanones are reduced by the complex metal hydrides of copper similarly to $LiAlH_4$ except with less selectivity.

PART IV. FUNCTIONAL GROUP SELECTIVITY AND STEREOSELECTIVITY INVOLVING MAGNESIUM-HYDROGEN COMPOUNDS

(IV-1) Functional Group Selectivity

The reducing properties of magnesium hydride and 2,6-diisopropylphenoxymagnesium hydride have been demonstrated for the first time. The above hydrides have been shown to reduce benzaldehyde, 4-tert-butylcyclohexanone, 1-iodooctane, ethyl benzoate, benzoyl chloride, 2,2,6,6-tetramethyl-trans-4-hepten-3-one as well as other organic molecules with representative functionality. These hydrides have been found to be inert to 1-octene, phenylethyne, 1-bromodecane, 1-chlorodecane and iodobenzene.

(IV-2) Stereoselective Reduction

The stereochemistry of reduction of the representative ketones, 4-tert-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, 2-methylcyclohexanone and camphor by magnesium hydride, alkoxyl magnesium hydrides (such as CH_3OMgH, i-PrOMgH, t-BuOMgH, Ph_3COMgH,  -OMgH,  -OMgH,  -OMgH, and  -OMgH), dialkylaminomagnesium hydrides (such as n-Pr_2NMgH, (i-Pr)(Me)NMgH, i-Pr_2NMgH, s-Bu_2NMgH, NMgH, NMgH and (Me_3Si)(t-Bu)NMgH), and trihydridomagnesium derivatives (such as H_3Mg_2O, H_3Mg_2O, H_3Mg_2O, H_3Mg_2OMe and $H_3Mg_2NPr_2^n$) has been determined. High stereoselectivity by some of the magnesium hydride derivatives was obtained and these results have been discussed.

PART V. REACTIONS OF LITHIUM ALUMINUM HYDRIDE-TRANSITION METAL HALIDES WITH ALKENES, ALKYNES AND ALKYL HALIDES

Admixtures of $LiAlH_4$ and first row transition metal chlorides were found to be excellent reagents for the reduction of alkenes, alkynes, and organohalides. The reactivity of the individual reagents varied depending on the metal halide. Eight alkenes, four alkynes, and twelve organohalides were involved in these studies. The results show that $LiAlH_4$ admixed with $FeCl_2$, $CoCl_2$, $NiCl_2$, and $TiCl_3$ are very promising reagents for the reduction of alkenes and halides. The reduction of alkynes to yield the alkenes or the alkanes depends on the metal halide, the ratio of reagent to substrate, the reaction temperature and the reaction time. $LiAlH_4$-$NiCl_2$ was found to be the best reagent to convert alkyne substrates to the corresponding alkenes selectively. A reduction mechanism involving cis addition was observed.

PART VI. SELECTIVE REDUCTION OF ALKYNES BY MgH_2-CuI AND MgH_2-CuO-<u>t</u>-Bu

Five terminal and internal alkynes were allowed to react with the new reagents, MgH_2-CuI and MgH_2-CuO-<u>t</u>-Bu. The corresponding 1-alkene or <u>cis</u>-alkene was the only product observed for the reduction of terminal alkynes or internal alkynes, respectively.

PART I

THE EVALUATION OF HYDRIDE REAGENTS FOR CONJUGATE REDUCTION OF ENONES

CHAPTER I

INTRODUCTION

Background

Catalytic hydrogenation[1] (H_2/Pd-C) and dissolving metal reduction[2] (Na-liq. NH_3) are the most common methods for effecting conjugate reduction of enones. The shortcomings of these methods are mainly inconvenience and in many cases low yields. Recently, LiCuRH[3] and $KB(\underline{sec}\text{-}Bu)_3H$[4] have been reported as effective reagents for conjugate reduction of enones. However, in the former case the reagent is quite difficult to prepare whereas in the latter case only 1,2 reduction is observed when β-substituents are present in the enone.

It is also well known that $LiAlH_4$ favors 1,2 reduction of enones[5]. On the other hand, the reactivity of $LiAlH_4$ can be substantially modified by the addition of metal salts. In this connection $LiAlH_4$-$AlCl_3$ has found unusual applicability in epoxide reductions[6], $LiAl(OCH_3)_3H$-CuI can effect reductive removal of halo and mesyloxy groups[7], and $LiAlH_4$-$TiCl_3$ has been found to be an excellent coupling reagent[8]. Furthermore, CuI has been used as a catalyst to carry out 1,4 alkylation in the reaction of Grignard reagent with enones[9]. The combination of $LiAlH_4$-CuI has been chosen as a starting point for the studies of regioselective reduction of enones.

Purpose

The ability of $LiAlH_4$ in admixture with certain metal halides, *e.g.* CuI, CuBr, CuCl, $TiCl_3$, $HgCl_2$, HgI_2 and $FeCl_3$ to effect conjugate reduction of enones is the purpose of this part of this thesis. The reactive intermediates of $LiAlH_4$-metal halides, the mechanism, and factors to control the regioselectivity of enones are also to be investigated.

CHAPTER II

EXPERIMENTAL

General Considerations

Manipulations of air-sensitive compounds were performed under nitrogen in a glove box equipped with a recirculating system using manganeous oxide columns to remove oxygen and dry ice-acetone to remove solvent vapors[10]. Reactions were performed under nitrogen at the bench using Schlenk tube techniques[11]. Syringes equipped with stainless steel needles were used for transfer of reagents.

Materials

Fisher Reagent Grade anhydrous diethylether 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 Et_2O for at least 24 hours followed by filtration through a fritted glass funnel in the dry box. The clear solution was standardized for aluminum content by EDTA.

Cuprous iodide (Fisher) was purified by dissolving it in saturated potassium iodide solution followed by treatment with decolorizing charcoal, filtration and precipitation by dilution with water. The purified CuI was collected and washed with absolute EtOH and dry Et_2O in the dry box[12].

Anhydrous ferric chloride (Fisher Sublimed) and titanium trichloride (Alfa) were opened only in the dry box and used without further purification.

Mercuric iodide and chloride were dried by heating at 90-100° under vacuum for 4 hours and standard THF solutions of these salts were prepared in the dry box.

2,2,6,6-Tetramethyl-trans-4-heptene-3-one, mp 43-43.7°C, NMR: (CCl_4), δ6.2-7.0 (2H,q,olefinic), δ1.1 (18H,s,two t-butyl) and its cis isomer were obtained from co-workers, J. R. Boone and T. L. Wiesemann.

An authentic sample of 2,2,6,6-tetramethyl-3-heptanone was synthesized by reaction of 2,2,6,6-tetramethyl-trans-4-hepten-3-one with Li/HMPA[14]; bp 108 C/2mmHg; NMR: (CCl_4), δ2.36 (2H,t,O=C-CH_2), δ1.40 (2H,t,CH_2), δ1.08 (9H,s,t-butyl) and δ0.87 (9H,s,t-butyl); IR: 1710 cm^{-1} (C=O), no hydroxyl absorption, Mass spectrum: M^+ 170.

2,2,6,6-Tetramethyl-trans-4-hepten-3-ol was obtained by reaction of 2,2,6,6-tetramethyl-trans-4-hepten-3-one with $LiAlH_4$: NMR: (CCl_4), δ5.5 (2H,m,olefinic), δ3.57 (1H,d,O-C-H), δ1.5 (1H,s,OH), δ0.98 (9H,s, t-butyl) and δ0.78 (9H,s,t-butyl); IR: 3600-3200 cm^{-1} (-OH), 1485 and 1470 cm^{-1} (C=C), no carbonyl absorption.

Mesityl oxide (Eastman), trans-3-penten-2-one, trans-3-penten-2-one, chalcone (Aldrich), 4-tert-butylcyclohexanone (Friton) and 3,3,5-trimethylcyclohexanone (Chemical Samples Co.) were purified by vacuum distillation or sublimation.

Isophorone, 2-cyclohexen-2-one, 2-cyclopentenone, and methyl vinyl ketone were purchased from Aldrich Chemical Company and used without further purification.

Iso-propyl alcohol and tert-butyl alcohol (Fisher) were purified by distillation over CaH_2.

Di-n-butyl amine and di-i-propyl amine (Fisher) were purified by distillation over NaOH.

Aluminum chloride and aluminum iodide (Fisher) were sublimed under vacuum and collected in the dry box. Aluminum iodide was stored in the refrigerator.

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

Instrumentation and Techniques

GLPC analyses were performed on F and M models 700 and 720 gas chromatographs.

NMR spectra were obtained on Varian A-60 and T-60 spectrometers.

Infrared absorptions were recorded on a Perkin Elmer Model 237B grating infrared spectrophotometer.

Mass spectra were obtained on a Varian Model M-66 mass spectrometer.

Lithium was determined by flame photometry (Coleman model 21).

Hydride was determined using a standard vacuum line equipped with a gas burette, Toepler pump and separation traps.

Boron analysis was accomplished by the titration of boric acid-mannitol with standard NaoH[15].

Aluminum was determined by EDTA titration.

Preparation of Reagents

AlH_3 was prepared by the reaction of 100% H_2SO_4 with $LiAlH_4$ in THF at low temperature (dry ice temperature) and filtered in the dry box[16]. Analysis: Li:Al:H=0.02:1.0:3.0.

H_2AlI was obtained by adding I_2 in THF solution to AlH_3 in THF at 0° stoichimetrically. The resulting solid was then filtered and washed carefully with dry THF. $HAlI_2$, H_2AlBr, $HAlBr_2$, H_2AlCl and $HAlCl_2$ were prepared by the distribution reactions of AlH_3 and AlI_3, $AlBr_3$ or $AlCl_3$[17]. These reagents were characterized by analyzing Al and H^-. The ratio for each reagent was within experimental error.

H_2BI and HBI_2 in THF were synthesized by adding stoichiometric amount of I_2 in THF to BH_3 in THF at 0°C. Boron and hydride were analyzed for each preparation, the ratio agreed with that calculated. The IR showed 2460 cm^{-1} for HBI_2 in THF; 2370 cm^{-1} and 2490 cm^{-1} for H_2BI in THF.

$H_2AlO\underline{t}$-Bu, $HAl(O\underline{t}\text{-Bu})_2$, $H_2AlO\underline{i}$-Pr, $HAl(O\underline{i}\text{-Pr})_2$, $H_2AlN(\underline{n}\text{-Bu})_2$, $HAl[N(\underline{n}\text{-Bu})_2]_2$, $H_2AlN(\underline{i}\text{-Pr})_2$ and $HAl[N(\underline{i}\text{-Pr})_2]_2$ were prepared by simply adding the appropriate alcohol or amine to AlH_3 in THF in a 1:1 or 2:1 molar ratio. Hydrogen was evolved during the addition and the reaction was complete within 15-20 minutes except in the case of the reaction involving $i\text{-}Pr_2NH$, in which case 3 hours reaction time was required. The $HAlX_2$ compounds studies were identified by their Al-H stretching frequency assignments;[18] $HAl(O\underline{t}\text{-Bu})_2$, 1850 cm^{-1}; $HAl(O\underline{i}\text{-Pr})_2$, 1845 cm^{-1}; $HAl[N(\underline{n}\text{-Bu})_2]_2$, 1820 cm^{-1}; $HAl[N(\underline{i}Pr)_2]_2$, 1810 cm^{-1}. In no case were the Al-H bands for AlH_3 or H_2AlX observed.

Reduction Procedures

Generally, a 10 ml Erlenmeyer flask with a Teflon coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen flush. CuI, CuCl, $TiCl_3$ or $FeCl_3$ (ca. 2mmoles) was transferred to the flask in the dry box; it was sealed with a rubber septum, removed from the dry box and connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil-filled bubbler. Four ml THF or Et_2O solvent was introduced into the reaction vessel and temperatures were regulated by ice-water (0°C), dry ice-acetone (-78°C) or dry ice-carbon tetrachloride (-20°C). A known amount of $LiAlH_4$ solution was then added to the slurry. An addition, a deep black color, was immediately produced with gas evolution except in the case of CuI at -78°C. After an indicated period, enone with internal standard, $\underline{n}$-$C_{12}H_{26}$, was added dropwise. After the designated reaction time, the reaction mixture was quenched with a minimum of distilled water and the resulting solution dried over $MgSO_4$. Analysis of the product and yield data were obtained by glc.

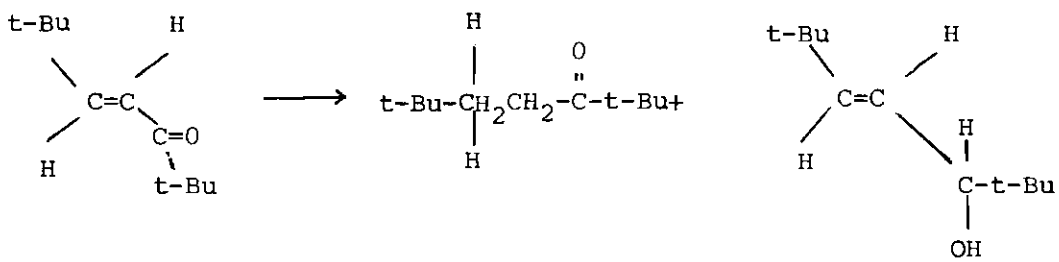
The reagents, $H_2AlO\underline{t}$-Bu, $HAl(O\underline{t}\text{-Bu})_2$, $H_2AlO\underline{i}$-Pr, $HAl(O\underline{i}\text{-Pr})_2$, $H_2AlN(\underline{n}\text{-Bu})_2$ and $HAl[N(\underline{i}\text{-Pr})_2]_2$, were prepared fresh for each reaction. $HAl[N(\underline{i}\text{-Pr})_2]_2$, $H_2AlN(\underline{i}\text{-Pr})_2$, H_2BI and HBI_2, which are stable at 0°C or room temperature for a considerable period of time, were prepared and stored in a refrigerator. Enone reductions were carried out by syringing known concentrations of reagent into a 10 ml Erlenmeyer flask, then adding the designated amount of enone, following the procedure described in the above paragraph. In some cases, the completion of the reaction was monitored by removing aliquot samples periodically and analyzed by glc.

A 10 ft. 5% Carbowax 20 M on Chromosorb W or a 15 ft. 10% Carbowax 20 M on chromosorb W was used to separate the reduction products of 2,2,6,6-tetramethyl-trans-4-hepten-3-one (I) (100°C), 2,2,6,6-tetramethyl-cis-4-hepten-3-one (II) (100°C), mesityl oxide (III) (80°C), 3-methyl-3-penten-3-one (V) (85°C), chalcone (V) (230°C), 2-cyclohexen-1-one (VI) (110°C), isophorone (VII) (110°C), 4-phenyl-3-buten-2-one (VIII) (180°C), methyl vinyl ketone (IX) (45°C) and 2-cyclopentenone (X) (80°C). Hydrocarbons ($\underline{n}$-$C_{12}H_{26}$ or $\underline{n}$-C_8H_{18}) were used as internal standards for each enone except enone VIII (internal standard, dodecyl alcohol). Retention times of the products varied slightly depending on glc conditions including the different columns used. For enones I-X, the order of elution was always the same: the 1,4 reduction product first; the enone second; and 1,2 reduction product last. The response ratio of each product was found by injecting the known molar ratio of authentic sample with internal standard. The authentic sample of the third possible product, the saturated alcohol, was prepared by reacting the 1,4 reduction product with $LiAlH_4$. The glc retention time was always after but near the 1,2 reduction product. In no case was the saturated alcohol seen in the enone reductions.

Reduction of 4-tert-butylcyclohexanone and 3,3,5-trimethylcyclohexanone was carried out by a similar procedure as described for enones. A 10 ft. column of 5% Carbowax 20 M on Chromosorb W was used to separate the products of 4-tert-butylcyclohexanone (130°C, internal standard $\underline{n}$-$C_{16}H_{34}$). The order of elution was ketone, axial alcohol, equatorial alcohol.

CHAPTER III

RESULTS AND DISCUSSION



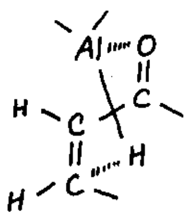
(1,4 reduction product) (1,2 reduction product) (1)

The effect of $LiAlH_4$-CuI on enone I has been studied in detail and the results are shown in Table 1. Since $LiAlH_4$ (runs 1 and 2) and $LiAlH_4$-CuI (catalytic amount of CuI, run 3) give mostly 1,2 reduction, the 1,4 reduction product is assumed to arise from the action of a species other than $LiAlH_4$. A wide variety of stoichiometric ratios of $LiAlH_4$:CuI:enone (runs 4-19) were studied and it was found that a ratio of 1:4:1 gives the best results under the conditions that $LiAlH_4$ and CuI are allowed to react 3 minutes before the addition of enone. At this stoichiometric ratio enone I was reduced in quantitative yield and 100% regioselectivity to the conjugate reduction product in THF at 0° when the reaction was allowed to proceed for 1 hour. Stoichiometry relating the reactive species to ketone is important (runs 14-16) since a significant amount of enone is recovered unreacted when the $LiAlH_4$:CuI:enone ratio is 1:4:4 or 1:4:2. When the $LiAlH_4$-CuI is 1:1 or 1:2, a significant amount of 1,2 product or unreacted ketone or both are observed (runs 4-11).

When $LiAlH_4$ and CuI are mixed at 0° in THF, a deep black color immediately results with some gas evolution. It was found that ~3 minutes reaction time is required (runs 17-19) for all of the $LiAlH_4$ to be consumed so that no 1,2 reduction product is observed. Reaction of the active reagent with the enone appears to be over in 30-60 minutes.

Temperature studies clarify the stablity of the $LiAlH_4$-CuI reagent. No reaction between $LiAlH_4$ and CuI occurs at -78° (run 26), slow reaction at -20° with some 1,2 reduction and recovered enone (run 27), and partial decomposition of the active reagent at room temperature (run 28). When $LiAlH_4$ and CuI were mixed at 0° and then cooled to -78°, no reaction took place as evidenced by complete recovery of the enone (run 26). On the other hand, generation of the active reagent at 0° followed by cooling to -20° before enone addition (run 27) resulted in 84% reaction with 100% regioselective formation of the conjugate reduction product. Since 10% ketone was recovered, it is clear that reduction of the substrate at -20° has no advantage over reduction at 0°. On the other hand, when the reagent was generated at 0° and allowed to warm to room temperature, 67% conjugate reduction product was observed with 29% recovery of the ketone. Apparently enough of the reagent decomposes at room temperature that a substantial amount of the starting material is recovered. It appears then, that the optimum temperature for generation of the reagent and addition of the substrate is 0°.

The optimum conditions (1:4:1 stoichiometry, 0°, THF) have been applied to other enones (III, IV, V and VI). The yields are generally high and the regioselectivity is 100%. However, the slower reaction rate for cis-enone (II) and the observation of no reaction with cyclohexenone and 3,3,5-trimethylcyclohexenone suggests to use a mechanism involving a six center transition state (A). It is more difficult for



(A)

the rigid cyclohexenone systems, cis-enones and trans-enones possessing disubstitution at the β-carbon of the enone to accomodate such a transition state (A) and hence these kinds of compounds should react more slowly.

Reduction of enone I and III (Table 2) with $LiAlH_4$-$TiCl_3$ was found not to be as effective as reduction with $LiAlH_4$-CuI. As might have been expected, the most effective ratio of $LiAlH_4$:$TiCl_3$ was different from that found for $LiAlH_4$-CuI. Also, one might expect that the optimum reaction temperature would be different since the active titanium species would be expected to have different stability and different reactivity characteristics compared to the copper reagent. It appears that optimum results are obtained using a $LiAlH_4$:$TiCl_3$:enone ratio of 1:1:1 at room temperature for 30 minutes (yield 63%). Lower reaction temperatures (0°) for enone I produced a substantial amount of 1,2-reduction product and a wide variation in reactant stoichiometry and reaction time seemed to have either little or adverse effect on the desired results.

Reduction of enone III with $LiAlH_4$-$TiCl_3$ was correspondingly lower than that observed for $LiAlH_4$-CuI. The best conditions of stoichiometry, temperature, and reaction time were similar to that observed for enone I except that the yields were lower (~33%).

$LiAlH_4$ was allowed to react with $FeCl_3$ at -78°, 0° and room temperature followed by addition of enone I. In no case did the enone react.

Two other metal salts, HgI_2 and $HgCl_2$, were also admixed with $LiAlH_4$ (Table 3). The regioselectivity was dependent on the ratio of $LiAlH_4$:HgX_2 and also on the halide. When the metal halide was changed from HgI_2 to $HgCl_2$, the unusual regioselectivity was lost corresponding to the same trend observed when the salt was changed from CuI to CuCl.

Since $LiAlH_4$-CuI and $LiAlH_4$-$TiCl_3$ produced a species in solution different from either of the reactants, and gave 100% regioselectivity, it was decided to evaluate these reagents as stereoselective reducing agents. Both $LiAlH_4$-CuI and $LiAlH_4$-$TiCl_3$ were allowed to react with 4-<u>tert</u>-butylcyclohexanone (VII) and 3,3,5-trimethylcyclohexanone (VIII) in THF. The results of Table 4 show both reagents gave considerably more equatorial attack compared to $LiAlH_4$ and that the $LiAlH_4$-$TiCl_3$ reagent gave considerably more equatorial attack than did $LiAlH_4$-CuI reagent on each ketone.

The unusual effectiveness of the reagent, $LiAlH_4$-CuI for conjugate reduction of the enones, encouraged the study of the nature of this reagent in solution. It was found that reactive intermediate is H_2AlI and not CuH or $CuAlH_4$.[19] Equation (2) explains the observation of a black precipitate and gas evolution when this reaction is carried out. The compound H_2AlI, was synthesized independently and was found to produce the same results as observed with $LiAlH_4$-CuI (1:4) (run 75). Actually, after most of these studies were complete, it was found the

$$LiAlH_4 + 2CuI \longrightarrow H_2AlI + LiI + 2Cu^\circ + H_2 \qquad (2)$$

1:4 ratio of $LiAlH_4$-CuI is not necessary. When the mixing period for $LiAlH_4$ and CuI was changed from 3 to 20 minutes (runs 11 and 73), it was found that the enone was reduced in 98% and 100% regioselectivity.

Since H_2AlI was found to react just as the reagent $LiAlH_4$-CuI, it was decided to evaluate other halogenaluminum hydrides. The author prepared the compounds H_2AlI, $HAlI_2$, H_2AlBr, $HAlBr_2$ and H_2AlCl and $HAlCl_2$, and it was expected that for steric reasons the $HAlX_2$ compounds would be more regioselective than the H_2AlX compounds and the regioselectivity of the reduction would decrease as the steric requirement of the halogen decreases (I>Br>Cl). It is clear from Table 5 that, indeed, the iodo compounds are more selective than the bromo or chloro compounds and the $HAlI_2$ is also highly regioselective. However, due to the steric requirement of $HAlI_2$, the reaction with enone I is much slower compared to H_2AlI and, hence, is not as attractive a reagent. Because $HAlI_2$ reacts so slowly the regioselectivity suffers slightly probably due to the small equilibrium amount of AlH_3 expected in THF solutions of $HAlI_2$.

Systematic studies of the haloalanes, H_nAlX_{3-n} (where n=1 or 2 and X=I,Br,Cl) reveal that the steric effect of the X-group is the most important factor in determining regioselectivity, i.e. $H_2AlI > H_2AlBr > H_2AlCl$, and also suggests that other alane derivatives containing bulky "X" groups, e.g., $HAl(\underline{i}\text{-}Bu)_2$, $HAl[N(\underline{n}\text{-}Bu)_2]_2$, $HAl[N(\underline{i}\text{-}Pr)_2]_2$, $HAl(O\underline{i}\text{-}Pr)_2$, $HAl(O\underline{t}\text{-}Bu)_2$. Boron derivatives containing a smaller central atom would also be expected to be highly regioselective reagents.

AlH_3, $H_2AlO\underline{t}\text{-}Bu$, $HAl(O\underline{t}\text{-}Bu)_2$, $H_2AlO\underline{i}\text{-}Pr$, $HAl(O\underline{i}\text{-}Pr)_2$, $H_2AlN(\underline{n}\text{-}Bu)_2$, $HAl[N(\underline{n}\text{-}Bu)_2]_2$, $H_2AlN(\underline{i}\text{-}Pr)_2$, $HAl[N(\underline{i}\text{-}Pr)_2]_2$, H_2BI and HBI_2 were freshly prepared for each reaction and allowed to react with enone I. The results are shown in Table 6. Enone (I) was reduced by AlH_3 without specific selectivity (50:48) at H^-:enone=3 and with improved regioselectivity (76:16) at H^-:enone=1 (runs 85 and 86). Clearly greater regioselectivity at H^-:enone=1 is expected since the steric requirement of the reagent increases from AlH_3 to H_2AlOR to $HAl(OR)_2$ during the course of the reaction.

The use of $HAl(\underline{i}\text{-}Bu)_2$ (run 87) results in greater regioselectivity (90:6) compared to AlH_3, but still not as good as hoped for. Experiments 88-91 show $HAl(O\underline{t}\text{-}Bu)_2$ is more selective than $H_2AlO\underline{t}\text{-}Bu$ and that significantly greater selectivity is experienced at 0° compared to room temperature. Excellent regioselectivity (98:1) is observed for $HAl(O\underline{t}\text{-}Bu)_2$ at 0°, however, the time required for complete reaction is long (12 hours). On the other hand, when $HAl(O\underline{i}\text{-}Pr)_2$ was allowed to react with I at 0° for 3 hours (run 93), 100% yield and 100% regioselectivity was observed. Although $HAl[N(\underline{n}\text{-}Bu)_2]_2$ was reasonably selective towards I (90:4), $HAl[N(\underline{i}\text{-}Pr)_2]_2$ reduced I at 0° in 15 minutes in 100% yield and 100% regioselectivity (run 97). Furthermore, enone I was reduced by HBI_2 with 100% regioselectivity and quantitative yield at room temperature, 9 hours (run 101).

Table 7 shows the results of the reactions of these new reagents with a series of ketones. The three alanes $HAl(O\underline{t}\text{-}Bu)_2$, $HAl(O\underline{i}\text{-}Pr)_2$ and $HAl[N(\underline{i}\text{-}Pr)_2]_2$ reacted to give 94% regioselectivity with enones I, IV, V and VI. Since $HAl[N(\underline{i}\text{-}Pr)_2]_2$ and HBI_2 gave 100% regioselectivity when allowed to react with the same enones, further studies were carried out just with these two reagents. In the reaction of HBI_2 with enones, quantitative yields of conjugate reduction product were observed except in the cases of the cyclic ketones. On the other hand, $HAl[N(\underline{i}\text{-}Pr)_2]_2$ gave excellent results except in the cases of enones III and I in addition to the cyclohexenones VII and VIII. However, $HAl[N(\underline{i}\text{-}Pr)_2]_2$ gave excellent results with cyclopentenone (XI) whereas HBI_2 was ineffective with this compound.

CHAPTER IV

CONCLUSION

Reagents, $LiAlH_4$-CuI and AlH_3-CuI, were found to be effective for conjugate reduction of enones in high yield and 100% regioselectivity. Their reacting species, H_2AlI and its derivatives H_2AlX and $HAlX_2$ (X=I,Br and Cl) were synthesized independently and evaluated as conjugate reducing agents. The regioselectivity was found to decrease in the order of I>Br>Cl. Also, the bulky aluminum hydride derivatives, for example, $HAl(O\underline{t}\text{-Bu})_2$, $HAl(O\underline{i}\text{-Pr})_2$ and $HAl[N(\underline{i}\text{-Pr})_2]_2$, were synthesized and shown that highly effective conjugate reduction depended on the steric requirement of the reagents. A six center transition state for the conjugate enone reduction was concluded to be operative.

Table 1. Reduction of Enones with $LiAlH_4$-CuI in THF

Exp.	Enone	Molar Ratio $LiAlH_4$	Molar Ratio CuI	Molar Ratio Enone[b]	Temp (°C)	Enone (%) Recovered	Products (%)[a] 1,4	Products (%)[a] 1,2
1	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	0	4.0	0	12	3	83
2	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	0	1.0	0	0	0	99
3	t-BuCH=CHC(=O)-Bu^t trans (I)	0.42	0.01	1.0	0	0	7	92
4	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	1.0	2.0[c]	0	0	40	50
5	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	1.0	1.0	0	0	64	27
6	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	1.0	0.5	0	0	49	~44

Table 1. (Continued)

Exp.	Enone	Molar Ratio LiAlH$_4$	CuI	Enone[b]	Temp (°C)	Enone (%) Recovered	Products (%)[a] 1,4	1,2
7	$\text{t-BuCH=CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-Bu}^t$ trans (I)	1.0	2.0	4.0[c]	0	54	46	6
8	$\text{t-BuCH=CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-Bu}^t$ trans (I)	1.0	2.0	2.0[c]	0	6	81	9
9	$\text{t-BuCH=CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-Bu}^t$ trans (I)	1.0	2.0	2.0[c,d]	0	0	58	34
10	$\text{t-BuCH=CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-Bu}^t$ trans (I)	1.0	2.0	2.0[c]	RT	62	38	<1
11	$\text{t-BuCH=CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-Bu}^t$ trans (I)	1.0	2.0	1.0	0	0	95	6
12	$\text{t-BuCH=CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-Bu}^t$ trans (I)	1.0	2.0	0.5	0	0	82	~1

Table 1. (Continued)

Exp.	Enone	Molar Ratio LiAlH$_4$	CuI	Enone[b]	Temp (°C)	Enone (%) Recovered	Products (%)[a] 1,4	1,2
13	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	3.0	1.0	0	0	87	7
14	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	4.0	4.0	0	69	26	0
15	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	4.0	4.0[e]	0	20	21	59
16	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	4.0	2.0	0	21	69	0
17	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	4.0	1.0[c]	0	0	82	7
18	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	4.0	1.0[f]	0	0	69	16

Table 1. (Continued)

Exp.	Enone	Molar Ratio LiAlH$_4$	Molar Ratio CuI	Molar Ratio Enone[b]	Temp (°C)	Enone (%) Recovered	Products (%)[a] 1,4	Products (%)[a] 1,2
19	t-BuCH=CHC(O)-Bu^t trans (I)	1.0	4.0	1.0	0	0	99	0
20	t-BuCH=CHC(O)-Bu^t trans (I)	1.0	4.0	1.0[d]	0	0	78	20
21	t-BuCH=CHC(O)-Bu trans (I)	1.0	4.0	1.0[c]	RT	0	63	24
22	t-BuCH=CHC(O)-Bu^t trans (I)	1.0	4.0	1.0	RT	47	34	<1
23	t-BuCH=CHC(O)-Bu^t trans (I)	1.0	4.0	4.0	-30	47	38	7
24	t-BuCH=CHC(O)-Bu^t trans (I)	1.0	4.0	1.0	-20	0	88	11

Table 1. (Continued)

Exp.	Enone	Molar Ratio LiAlH$_4$	CuI	Enone[b]	Temp (°C)	Enone (%) Recovered	Products (%)[a] 1,4	1,2
25	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	4.0	1.0	-78	0	0	93
26	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	4.0	1.0	0→ -78[g]	101	0	0
27	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	4.0	1.0	0→ -20[g]	10	84	0
28	t-BuCH=CHC(=O)-Bu^t trans (I)	1.0	4.0	1.0	0→ RT[h]	29	67	~1
29	t-BuCH=CHC(=O)-Bu^t cis (II)	1.0	4.0	1.0	0	33	40	0
30	$(CH_3)_2C$=CHC(=O)-CH_3 (III)	1.0	4.0	1.0	0	3	66	~1

Table 1. (Continued)

Exp.	Enone	Molar Ratio LiAlH$_4$	CuI	Enone[b]	Temp (°C)	Enone (%) Recovered	Products (%)[a] 1,4	1,2
31	$(CH_3)_2C{=}CH\overset{O}{\overset{\|}{C}}{-}CH_3$ (III)	1.0	4.0	0.5	0	8	70	0
32	$CH_3CH{=}C(CH_3)\overset{O}{\overset{\|}{C}}{-}CH_3$ (IV)	1.0	4.0	1.0	0	0	97	0
33	$CH_3CH{=}CH\overset{O}{\overset{\|}{C}}{-}CH_3$ (V)	1.0	4.0	1.0	0	0	78	0
34	$PhCH{=}CH\overset{O}{\overset{\|}{C}}{-}Ph$ (VI)	1.0	4.0	1.0	0	0	101	0

a. Product is based on ketone used. Reaction time for all reactions is 30-60 min., counted from ketone addition.

b. All reaction mixtures were stirred for 3 min. between LiAlH$_4$ addition and ketone addition, except when noted.

c. LiAlH$_4$ was added rapidly, stirred 1 min., then the ketone added dropwise.

Table 1. (Continued)

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d. Et_2O was used instead of THF.
e. $LiAlH_4$ was added to the ketone-CuI mixture.
f. Same as (c), but interval was 10 sec.
g. $LiAlH_4$ was added at 0°, ketone was added at -78° or -20°.
h. Stirred at RT for 10 min. before ketone addition.

Table 2. Reduction of Enones with $LiAlH_4$-$TiCl_3$ in THF

Exp.	Enone	Molar Ratio $LiAlH_4$	Molar Ratio $TiCl_3$	Molar Ratio Enone	Temp (°C)	Reaction Time	Enone Recovered	Products (%) 1,4	Products (%) 1,2
35	I	2.0	1.0	1.0	0	1 hr	0	12	70
36	I	1.0	1.0	1.0	0	1 hr	0	13	53
37	I	1.0	2.0	1.0	0	1 hr	0	46	24
38	I	1.0	3.0	1.0	0	1 hr	0	29	34
39	I	1.0	1.0	1.0	RT	10 min	0	53	0
40	I	1.0	1.0	1.0	RT	30 min	0	63	0
41	I	1.0	1.0	1.0	RT	1 hr	0	58	0
42	I	1.0	1.0	1.0	RT	1.5 hr	0	55	0
43	I	1.0	1.0	1.0	RT	12 hr	0	53	0
44	I	2.0	2.0	1.0	RT	1 hr	0	66	0
45	I	2.0	1.0	1.0	RT	1 hr	0	63	0
46	I	2.0	1.0	1.0	reflux	1 hr	0	60	0
47	I	4.0	4.0	1.0	RT	8 hr	0	46	0
48	I	1.0	2.0	1.0	RT	1 hr	0	29	~1

Table 2. (Continued)

Exp.	Enone	Molar Ratio $LiAlH_4$	$TiCl_3$	Enone	Temp (°C)	Reaction Time	Enone Recovered	Products (%) 1,4	1,2
49	I	1.0	2.0	1.0	RT	8 hr	0	35	0
50	I	1.0	2.0	1.0	RT→0[g]	1 hr	0	35	~1
51	I	3.0	4.0	1.0	RT	1 hr	0	18	25
52	I	1.0	3.0	1.0	RT	1 hr	0	14	0
53	I	3.0	1.0	1.0	RT	1 hr	0	28	41
54	I	2.0	2.0	1.0[f]	RT	10 min	0	6	31
55	III	1.0	1.0	1.0	RT→0[g]	1 hr	~1	34	0
56	III	1.0	2.0	1.0	RT→0[g]	1 hr	~2	18	0
57	III	2.0	2.0	1.0[i]	RT	1 hr	0	33	0
58	III	2.0	2.0	1.0[f]	RT	1 hr	9	0	25

i. Same as (f) in Table 1 but 60 min.

Table 3. Reduction of Enone I with $LiAlH_4$-HgI_2, $LiAlH_4$-$HgCl_2$ or $LiAlH_4$-CuCl in THF

Exp.	Molar Ratio $LiAlH_4$	HgI_2	Enone	Temp. (°C)	Enone Recovered (%)	Products 1,4	1,2
59	1.0	1.0	1.0	0	0	65	22
60	1.0	1.5	1.0	0	0	86	8
61	1.0	2.0	1.0	0	0	93	5
62	1.0	4.0	1.0	0	75	8	0
		($HgCl_2$)					
63	1.0	1.0	1.0	0	0	46	56
64	1.0	1.5	1.0	0	42	32	17
		(CuCl)					
65	1	4	1	0	55	32	4

Table 4. Stereoselective Reduction of 4-tert-Butylcyclohexanone (VII) or 3,3,5-Trimethylcyclohexanone (VIII) with $LiAlH_4$-CuI and $LiAlH_4$-$TiCl_3$ in THF

Exp.	Ketone	Molar Ratio $LiAlH_4$	:CuI (or $TiCl_3$)	:Ketone	Conditions	Ketone Recovered (%)	Relative Yield (%) ax-OH	eq-OH	Mass Balance
67	VII	1.5	0	1.0	0°, 2 hr	0	8	92	~100
68	VII	1.0	4.0 (CuI)	1.0	0°, 1 hr	0	29	71	~100
69	VII	1.0	1.0 ($TiCl_3$)	1.0	RT, 1 hr	0	70	30	81
70	VIII	1.5	0	1.0	0°, 2 hr	0	80	20	~100
71	VIII	1.0	4.0 (CuI)	1.0	0°, 1 hr	0	85	15	~100
72	VIII	1.0	1.0 ($TiCl_3$)	1.0	RT, 1 hr	0	97	3	74

Table 5. Reduction of Enone I with the Reagents: $LiAlH_4$-CuI, AlH_4-CuI, H_2AlI, $HAlI_2$, H_2AlCl and $HAlCl_2$ in THF

Exp.	Molar Ratio			Conditions	Enone (%) Recovered	Products (%)	
						1,4	1,2
	$LiAlH_4$	CuI	Enone[j]				
73	1	2	1	0, 15 min	0	98	0
	AlH_3	CuI	Enone[j]				
74	1	3	1	0, 15 min	0	99	<1
	H_2AlI	CuI	Enone[j]				
75	1	0	1	0, 1 hr	0	98	<0.5
76	1	0	1[d]	0, 1 hr	0	70	12
77	1	~10	1	0, 1 hr	77	11	0
	$HAlI_2$		Enone				
78	1		1	0, 1 hr	84	0.5	0
79	2		1	RT, 4 hr	33	59	5
80	4		1	RT, 1 hr	16	80	2
	H_2AlBr		Enone				
81	1		1	0, 1 hr	0	86	12

Table 5. (Continued)

Exp.	Molar Ratio		Conditions	Enone (%) Recovered	Products (%)	
					1,4	1,2
	$HAlBr_2$	Enone				
82	1	1	0°, 1 hr	0	92	6
	H_2AlCl					
83	1	1	0°, 10 min	0	86	15
	$HAlCl_2$	Enone				
84	2	1	0°, 1 hr	8	86	7

j. The mixing period of $LiAlH_4$-CuI or AlH_3-CuI was 20 min before enone addition.

d. Et_2O solvent.

Table 6. Reduction of 2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one (I) with $HAlX_2$ or HBI_2 Compound

Exp.	Alane or Borane	Mole Ratio Alane or Borane/Enone	Reaction Conditions	Enone Recovered	% Products[a] 1,4	% Products[a] 1,2
85	AlH_3	1:1	0°, 1 hr	0	50	48
86	AlH_3	1:3	0°, 1 hr	8	76	16
87	HAl(*i*-Bu)$_2$	1:1	0°, 1 hr	0	90	6
88	H_2AlO*t*-Bu	1:1	RT, 0.5 hr[b]	0	88	11
89	H_2AlO*t*-Bu	1:1	0°, 0.5 hr[b]	0	95	6
90	HAl(O*t*-Bu)$_2$	2:1	RT, 4 hr[b]	1	90	5
91	HAl(O*t*-Bu)$_2$	4:1	0°, 12 hr[b]	0	98	1
92	H_2AlO*i*-Pr	1:1	0°, 3 hr[c]	0	62	40
93	HAl(O*i*-Pr)$_2$	2:1	0°, 3 hr[c]	0	100	0
94	H_2AlN(*n*-Bu)$_2$	1:1	0°, 3 hr[c]	0	81	19
95	HAl[N(*n*-Bu)$_2$]$_2$	4:1	0°, 6 hr[c]	1	90	4
96	H_2AlN(*i*-Pr)$_2$	1:1	0°, 15 min[d]	0	94	5
97	HAl[N(*i*-Pr)$_2$]$_2$	2:1	0°, 15 min[d]	0	100	0

Table 6. (Continued)

Exp.	Alane or Borane	Mole Ratio Alane or Borane/Enone	Reaction Conditions	Enone Recovered	% Products[a] 1,4	1,2
98	BH_3	1:1	0°, 0.5 hr	0	78	11
99	BH_3	1:3	0°, 2 hr	0	94	7
100	H_2BI[e]	1:1	0°, 2 hr	2	92	6
101	HBI_2[e]	4:1	RT, 9 hr	0	100	0

a. Yields are absolute based on initial ketone using an internal standard. All reactions were performed on 1 mmole scale.

b. t-BuOH was added to AlH_3 dropwise and kept stirring 15 min. before use.

c. Same procedure as (b) but 60 min.

d. Same procedure as (b) but 3 hr.

e. I_2/THF was added to BH_3 and kept stirring for 1 hr. at 0°C.

Table 7. Reduction of Enones III-XI with $HAlX_2$ Reagents at 0° and HBI_2 at Room Temperature in THF

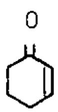
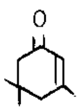
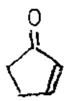
	Ratio of 1,4 to 1,2 Reduction				
	$HAl(i\text{-}Bu)_2$	$HAl(Ot\text{-}Bu)_2$	$HAl(Oi\text{-}Pr)_2$	$HAl[N(i\text{-}Pr)_2]_2$	HBI_2 [b]
$CH_3CH=CH-\overset{O}{C}-CH_3$ (V)	8:90	94:5	95:2	100:0	95:0
$CH_3CH=C(CH_3)\overset{O}{C}-CH_3$ (IV)	18:81	90:6	96:4	100:0.5	96:0
$PhCH=CH\overset{O}{C}Ph$ (VI)	63:35	98:0	97:2	100:0.5	95:0
$(CH_3)_2C=CH\overset{O}{C}CH_3$ (III)	--	--	--	6:0	98:0
 (VII)	--	--	--	23:72	5:0
 (VIII)	--	--	--	0:0	15:0
$PhCh=CH\overset{O}{C}CH_3$ (IX)	--	--	--	96:0	98:0

Table 7. (Continued)

	Ratio of 1,4 to 1,2 Reduction				
	$HAl(i\text{-}Bu)_2$	$HAl(Ot\text{-}Bu)_2$	$HAl(Oi\text{-}Pr)_2$	$HAl[N(i\text{-}Pr)_2]_2$	HBI_2 [b]
$CH_2{=}CH\overset{O}{\overset{\Vert}{C}}CH_3$ (X)	--	--	--	41:45	95:0
 (XI)	--	--	--	94:1	11:0

a. $HAl(Ot\text{-}Bu)_2$:enone = 6, $HAl(Oi\text{-}Pr)_2$:enone = 6, $HAl[N(i\text{-}Pr)_2]_2$:enone = 4, $HAl(i\text{-}Bu)_2$:enone = 2.

b. HBI_2:enone = 8, 20 hours, room temperature.

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PART II

REACTIONS OF NEW ORGANOCUPRATES

(II-1) REGIOSELECTIVE METHYLATION OF ENONES

(II-2) SUBSTITUTION REACTIONS OF ALKYL, CYCLOALKYL AND ARYL HALIDES

(II-3) CONCERNING THE REACTION OF ORGANOCUPRATES WITH 4-*TERT*-BUTYLCYCLOHEXANONE

CHAPTER I

INTRODUCTION

Background

Lithium dialkylcuprates have been considered as very versatile reagents in organic synthesis.[1] Several recent reports have been concerned with unusual reactivity of reagents prepared by mixing lithium dialkyl- or diarylcuprates with the corresponding organolithium compounds. For example, the reagent having the stoichiometry $LiCuPh_2$-PhLi appears to be more reactive than $LiCuPh_2$ in metal-halogen exchange reactions and coupling with aryl bromides.[2] Also, it has been recently found that a 3:2 mixture of $LiCu(CH_3)_2$ and CH_3Li is more stereoselective toward 4-tert-butylcyclohexanone than either $LiCu(CH_3)_2$ or CH_3Li.[3] In addition, mixtures of $LiCu(CH_3)_2$ and CH_3Li have been found to react with diaryl ketones as if a reducing agent more powerful than either $LiCu(CH_3)_2$ or CH_3Li is present.[4] These reports suggest that lithium diorganocuprates and organolithium compounds are capable of reacting to form complexes of the type $Li_2Cu(CH_3)_3$ and $Li_3Cu(CH_3)_4$. Recently, evidence for the existence of new organocuprate species, $LiCu_2(CH_3)_3$ and $Li_2Cu(CH_3)_3$ in THF and $Li_2Cu(CH_3)_3$ and $Li_2Cu_3(CH_3)_5$ in Et_2O was obtained by a co-worker, J. J. Watkins.[5] In THF, $LiCu_2(CH_3)_3$ and $LiCu(CH_3)_2$ have been found to exist as pure stoichiometric compounds when the CH_3Li:CH_3Cu ratio was 1:2 and 1:1, respectively. When the CH_3Li:CH_3Cu ratio was 2:1, $Li_2Cu(CH_3)_3$ was formed as an equilibrium mixture containing $LiCu(CH_3)_2$ and CH_3Li. In Et_2O, evidence was presented to indicate the existence of $Li_2Cu_3(CH_3)_5$, $LiCu(CH_3)_2$ and $Li_2Cu(CH_3)_3$. The first two compounds can be prepared stoichiometrically pure. The latter compound is part of an equilibrium mixture.

Purpose

Owing to the current interest in organocopper reagents, it is proposed to evaluate these new cuprates as conjugate methylating agents toward α,β-unsaturated ketones. A study of the substitution reactions of these new cuprates with alkyl, cycloalkyl and aryl halides is also desired. Further, the previously reported unusual stereochemistry in the reaction of 4-_tert_-butylcyclohexanone with CH_3Li-$LiCu(CH_3)_2$[3] seems important and necessary to be reviewed since the evidence for the existence of $Li_2Cu(CH_3)_3$ has been obtained.

CHAPTER II

EXPERIMENTAL

Note: The cuprate reagents used for the reactions of the enones were prepared by J. J. Watkins of this laboratory.

Instrumentation and Techniques

Reactions were performed under nitrogen at the bench using Schlenk tube techniques.[6] Other manipulations were carried out in a glove box equipped with a recirculating system using manganeous oxide columns to remove oxygen and dry ice-acetone to remove solvents vapors.[7] Proton NMR spectra were obtained at 60 MHz using a Varian A-60 NMR spectrometer. GLPC analyses were performed on the F and M model 700 or 720 gas chromatographs. The ^{13}C NMR spectra were obtained at 100 MHz with a JEOL Fourier transform spectrometer, Model PFT-100.

Analyses

Active CH_3 group analysis was carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line and collecting the evolved methane with a Toepler pump. Lithium was determined by flame photometry. Iodie was determined by the Volhard procedure. Copper was determined by electrolytic deposition on a platinum electrode.

Materials

Tetrahydrofuran (Fisher Certified Reagent Grade) was distilled under nitrogen from $NaAlH_4$ and diethyl ether (Fisher Reagent) from $LiAlH_4$ prior to use. Methyllithium in THF or Et_2O was prepared by the reaction of $(CH_3)_2Hg$ with excess lithium metal. Both solutions were stored at -78° until ready to use. Cuprous iodide was purified by precipitation from an aqueous KI-CuI solution.[8] The precipitated solid was washed with water, ethanol, and diethyl ether and then dried at room temperature under reduced pressure. The enones:2,2,6,6-tetramethyl-trans-4-hepten-3-one, trans-3-methyl-3-penten-2-one, mesityl oxide, 2-cyclohexen-1-one and isophorone were obtained from the same source described in Part I.

The organohalides, 1-iododecane, 1-bromodecane, 1-chlorodecane, 1-fluorodecane, 6-bromo-1-hexene, 6-chloro-1-hexene, iodocyclohexane, bromocyclohexane, chlorocyclohexane, iodobenzene, bromobenzene, chlorobenzene, fluorobenzene, p-chloroanisole, p-fluoroanisole, 1-chlorocyclohexene and 3-chlorocyclohexene were purchased from Eastman, Fisher, Aldrich or Frinton companies and used without further purification. Lithium salts:lithium perchlorate, lithium iodide, and lithium bromide were purchased from Alfa Inorganics and dried under vacuum at 100°C overnight. Solutions of these salts in THF or Et_2O were prepared in a dry box. 4-tert-Butylcyclohexanone and 2-methylcyclohexanone were obtained commercially and purified by sublimation or distillation under the vacuum.

Preparation of Reagents in THF

$LiCu_2(CH_3)_3$. Cuprous iodide (1.53 grams, 8.05 mmoles) was weighed into a 50 ml round bottom flask in the dry box, then the flask fitted with a rubber septum. The flask was removed from the dry box, connected by means of a needle to a nitrogen bubbler, and 15 ml of THF added in order to slurry the solid. The slurry was cooled to -78° and 15.1 ml of a 0.802 M solution of CH_3Li (12.1 mmoles) in THF was added to the flask. Within 5 minutes all of the solid had dissolved and a clear, brown solution was present. H^1 NMR at -96° showed only one signal for protons suggesting $LiCu_2(CH_3)_3$. Analysis of the solution showed Li, Cu, CH_3 and I to be present in the ratio 1.49:1.00:1.50:1.02.

$LiCu(CH_3)_2$. Cuprous iodide (1.26 grams, 6.62 mmoles) was allowed to react with 16.5 ml of 0.802 M CH_3Li (13.2 mmoles) in THF using the same procedure as was used to prepare $LiCu_2(CH_3)_3$ (see above). All the solid dissolved within one minute to yield a clear, light brown solution. H^1 NMR -96° showed only one signal at -1.57 δ, which corresponds to $LiCu(CH_3)_2$. An analysis of the solution showed Li, Cu, CH_3 and I to be present in the ratio 2.00:1.00:2.12:0.98.

$Li_2Cu(CH_3)_3$. Cuprous iodide (0.80 grams, 4.32 mmoles) was allowed to react with 19.0 ml of 0.802 (16.9 mmoles) in THF using the above procedure for making $LiCu_2(CH_3)_3$. All the solid dissolved within one minute to yield a clear, colorless solution. H^1 NMR at -96° showed the presence of $Li_2Cu(CH_3)_3$ in equilibrium with $LiCu(CH_3)_2$, and CH_3Li (four signals at -1.40, -1.57, -1.73 and -2.08 δ are observed; signals at -1.57 and -2.08 are due to $LiCu(CH_3)_2$ and CH_3Li, respectively, while those at -1.40 and -1.73 are due to $Li_2Cu(CH_3)_3$). An analysis of the solution showed Li, Cu, CH_3 and I to be present in the ratio 3.82:1.00: 3:62:0.94.

Preparation of Reagents in Et_2O

$LiCu(CH_3)_2$. Cuprous iodide (0.53 grams, 2.79 mmoles) was weighed into a 50 ml round bottom flask in the dry box, then the flask fitted with a rubber septum. The flask was removed from the dry box, connected by means of a needle to a nitrogen bubbler, and 5 ml of Et_2O added in order to slurry the solid. The slurry was cooled to -78° and 4.4 ml of 1.27 M solution of CH_3Li (5.58 mmoles) in Et_2O was added to the flask. All the solid dissolved immediately and a clear colorless solution formed. H^1NMR at -96° showed only $LiCu(CH_3)_2$ to be present. An analysis of the solution showed Li, Cu, CH_3 and I to be present in the ratio 1.97:1.00:1.96:0.95.

$Li_2Cu_3(CH_3)_5$. Cuprous iodide (0.380 grams, 2.0 mmoles) was allowed to react with 3.5 ml of 0.95 M solution of CH_3Li (3.3 mmoles) in Et_2O using the same procedure as was used to prepare $LiCu(CH_3)_2$ (see above). Most of the solid dissolved immediately to give a clear, light pink solution, but a small amount of yellow solid (methylcopper) remained. An analysis of the solution showed Li, Cu, CH_3 and I to be present in the ratio 5.21:3.00:5.09:3.03. If all of the iodide is assumed to be present as LiI, then the organocopper species would have a Li:Cu:CH_3 ratio of 2.18:3.00:5.09. This indicates the presence of the complex $Li_2Cu_3(CH_3)_5$. This compound was indeed shown to be present by NMR spectroscopy.[5]

$Li_2Cu(CH_3)_3$. Cuprous iodide (0.57 grams, 2.97 mmoles) was allowed to react with 9.36 ml of 1.27 M solution of CH_3Li (11.9 mmoles) in Et_2O using the same procedure as was used to prepare $LiCu(CH_3)_2$ (see above). All the solid dissolved immediately and a clear, colorless solution remained. H^1NMR at -96° showed $Li_2Cu(CH_3)_3$, $LiCu(CH_3)_2$ and CH_3Li to be present. An analysis of the solution showed Li, Cu, CH_3 and I to be present in the ratio 3.82:1.00:3.88:1.02.

$LiCu(CH_3)_2$-halide free. The preparation of halide free $LiCu(CH_3)_2$ was similar to that used for $LiCu(CH_3)_2$, except that CH_3Li was added to CuI in two steps. After the first equivalent mole of CH_3Li was added to the slurry CuI in THF or Et_2O to produce methylcopper as a yellow solid slurry, LiI was removed by centrifuging, decanting and washing with several portions of dry solvent. The second equivalent mole of CH_3Li was then allowed to react with the slurry of methylcopper to produce $LiCu(CH_3)_2$-halide free.

General Reactions of Enones

A 10 ml Erlenmeyer flask with a Teflon coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen flush, then sealed with a rubber septum and connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil filled bubbler. The cuprate reagent (ca. 0.1-0.5 mmole) was syringed into the flask, then the calculated amount of enone (in THF or Et_2O solvent with internal standard, $\underline{n}$-$C_{12}H_{26}$ or $\underline{n}$-$C_{14}H_{30}$) was added to the stirred reagent. After the designated reaction time, the reaction was quenched with H_2O slowly and dried over $MgSO_4$. A 10 ft. 5% Carbowax 20 M on Chromosorb W column was used to separate the 1,4 and 1,2 methylation products of enone I (120°C), enone II (90°C), enone III (100°C), enone IV (100°C), enone V (100°C) and enone VI (100°C). Authentic samples of 1,2-addition products were prepared by reaction of the enone with CH_3Li. The yield percent for each reaction with $LiCu(CH_3)_2$ was normalized by 100% yield = enone recovery % + 1,2 product % + 1,4 product %. The yield % for other reactions was based on the amount of $LiCu(CH_3)_2$ used in the reaction. Retention times of products varied slightly depending on glc conditions. However, for enones I-V, the order of elution was always the same: enone first; 1,4 methylation product second; and 1,2 methylation product last. The 1,2 methylation product of enone V had a shorter elution time than the 1,4 methylation product.

General Reactions of Halides

The experimental procedures are similar to those described in the reactions of enones. Two glc columns were used to separate the products: column A (10 ft. 5% Carbowax 20 M on Chromosorb W) and column B (6 ft. 10% Apiezon L 60-80 S). The following glc conditions (column, column temperature, internal standard) are described: *n*-decyl halides (column A, 110°C, *n*-$C_{12}H_{26}$); 6-bromo-1-hexene, 6-chloro-1-hexene, cyclohexyl halides, 1-chlorocyclohexene and 3-chlorocyclohexene (all column B, 55°C, *n*-C_8H_{18}); phenyl halides, p-chloro and p-fluoroanisole (all column B, 105°C, *p*-xylene). Using column B, (at 55°C, Helium flow rate 60 ml/min.) the following products can be separated. The elution is in the order of cyclohexane, cyclohexene, methylcyclohexane, 1-methyl-1-cyclohexene and *n*-octane. On the same column at 105°C, elution is in the order: toluene, *p*-xylene, anisole and *p*-methylanisole. The retention time and response ratio of the internal standards were corrected by comparison with authentic samples.

General Reactions of 4-*tert*-Butylcyclohexanone and 2-Methylcyclohexanone

A 10 ml Erlenmeyer flask with a Teflon coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen, then sealed with a rubber septum and connected by means of a needle to a nitrogen filled manifold equipped with a mineral oil filled bubbler. Methyl lithium (ca. 0.1-1.0 mmole) was syringed into the flask and the addition of lithium salt followed if needed. The temperature was controlled by dry-ice acetone bath, then the calculated amount of

4-*tert*-butylcyclohexanone or 2-methylcyclohexanone (in THF or Et_2O solvent with internal standard, *n*-$C_{14}H_{30}$) was added to the stirred reagent. After the designated reaction time, the reaction was quenched with methanol slowly and dried over $MgSO_4$. A 12 ft. 10% FFAP on Diatoport column (column temperature: 150°C, helium flow rate: 60 ml/min) was used to separate the products of 4-*tert*-butylcyclohexanone. The retention time was 13.4 min. for *n*-$C_{14}H_{30}$, 32.8 min. for *cis*-1-methyl-4-*tert*-butylcyclohexanol, 38.0 min. for 4-*tert*-butylcyclohexanone and 41.6 min. for *trans*-1-methyl-4-*tert*-butylcyclohexanol. The response ratio was 0.52 for both alcohols by measuring the peak area ratio of product to internal standard versus their molar ratio. A 12 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 min. for the ketone, 5.2 min. for the *cis*-alcohol, 9.5 min. for the *trans*-alcohol and 16.1 min. for *n*-$C_{14}H_{30}$. The response ratio was 0.54 for both alcohols.

CHAPTER III

RESULTS AND DISCUSSION

(III-1) Regioselective Methylation of Enones

Six enones (I-VI) were chosen to react with $LiCu(CH_3)_2$, $LiCu_2(CH_3)_3$ and $Li_2Cu(CH_3)_3$ in THF and $LiCu(CH_3)_2$, $Li_2Cu_3(CH_3)_5$ and $Li_2Cu(CH_3)_3$ in Et_2O solvent. The results of these reactions are shown in Tables 8 and 9. In THF solvent (Table 8), $LiCu_2(CH_3)_3$ reacted with enones in the same fashion as $LiCu(CH_3)_2$ to give 100% 1,4-regioselective methylation, but at a slower rate (exps. 2, 5, and 11). When the enone was substituted in the α position (enone III), $LiCu_2(CH_3)_3$ did not react under the conditions that $LiCu(CH_3)_2$ gave a 56% yield. On the other hand, $Li_2Cu(CH_3)_3$ has a reaction rate similar to that of $LiCu(CH_3)_2$ in the reactions of β-monosubstituted enones (I, II, III and V) but gives mostly 1,2 methylation for β-disubstituted enones such as IV (exp. 12). Although all three cuprate reagents gave quantitative conjugate alkylation with cyclohexenone (V) none of the three reagents reacted with isophorone (VI).

In Et_2O solvent (Table 9), the reactions are much faster than in THF solvent. $Li_2Cu(CH_3)_5$ is more reactive than $LiCu(CH_3)_2$ and also provides 100% 1,4 regioselectivity in each case studied as does $LiCu(CH_3)_2$. $Li_2Cu(CH_3)_3$ gives 100% conjugate alkylation for cyclohexenone (V) whereas $LiCu(CH_3)_2$ under the same conditions results in some recovered reactant. However, in diethyl ether, $Li_2Cu(CH_3)_3$ is in general less regioselective than $LiCu(CH_3)_2$. Clearly in the case of $Li_2Cu(CH_3)_3$, CH_3Li is reacting in diethyl ether to form 1,2-addition product.

It appears that the relative rates of $LiCu(CH_3)_2$, $LiCu_2(CH_3)_3$, $Li_2Cu_3(CH_3)_5$ and $Li_2Cu(CH_3)_3$ reaction with enones depends on the steric requirement of the particular enone. When the enone is disubstituted (either β,β or α,β) reaction is much slower than for a monosubstituted enone. For example, $LiCu_2(CH_3)_3$ does not react with III (an α,β-disubstituted enone) in THF whereas $LiCu(CH_3)_2$ effects conjugate addition in 56% yield. On the other hand, $LiCu_2(CH_3)_3$ and $LiCu(CH_3)_2$ react with II (β-monosubstituted enone) in THF at about the same rate (expts. 4 and 5). Clearly, all of the cuprates react with cyclohexenone (V) at a rapid rate compared to the other enones whereas isophorone (VI) (a β,β-disubstituted enone) does not react with any of the cuprates.

When $Li_2Cu(CH_3)_3$ was allowed to react with IV (a β,β-disubstituted enone) in THF, the reaction involving conjugate addition is apparently slowed down so much that 1,2 addition by the equilibrium concentration of CH_3Li becomes the major reaction. The same phenomenon is observed in diethyl ether (Table 9). $Li_2Cu(CH_3)_3$ is affected much more than $LiCu(CH_3)_2$ by disubstitution in the enone. For example, with the least substituted enones (II and V), $Li_2Cu(CH_3)_3$ gives conjugate addition in high yield, whereas with the more sterically hindered enones (I, III, IV and VI), substantial 1,2-addition takes place.

(III-2) Substitution Reactions of Alkyl-, Cycloalkyl- and Aryl Halides

Several organic halides were allowed to react with the new organocuprates and $LiCu(CH_3)_2$ in THF and Et_2O in order to compare the reactivities of the new cuprates and their yields in these reactions. Since $Li_2Cu(CH_3)_3$ is in equilibrium with $LiCu(CH_3)_2$ and CH_3Li, the reaction of CH_3Li in each case is also compared. Each reaction was carried out using excess reagent (10:1 molar ratio of active methyl: halide), room temperature and two solvents (THF and Et_2O). Since $LiCu_2(CH_3)_3$ is insoluble in Et_2O and $Li_2Cu_3(CH_3)_5$ is insoluble in THF, studies of these cuprates were not involved in these particular solvents. The results of these reactions are shown in Table 10.

In the reactions of 1-iododecane (expts. 1-7), each organocuprate reagent reacted similarly to produce the substitution product, n-undecane, usually in high yield. The shorter reaction time (10 min.) indicated that $Li_2Cu(CH_3)_3$ in THF reacted more rapidly than any of the other reagents. The metal-halogen exchange to form 50% n-decane in the reaction of CH_3Li with 1-iododecane suggests that in reactions involving $Li_2Cu(CH_3)_3$, the reaction species is $Li_2Cu(CH_3)_3$ and not one of its equilibrium components (e.g. CH_3Li). Our previous studies[5] have shown that $Li_2Cu(CH_3)_3$ forms an equilibrium mixture in THF and Et_2O as described by Equation (1).

$$Li_2Cu(CH_3)_3 \rightleftharpoons CH_3Li + LiCu(CH_3)_2 \qquad (1)$$

Methyllithium as well as the cuprates also reacted with 1-bromodecane to form undecane. The yields in the THF were quantitative after just one hour reaction time (Table 10, expts. 8-14), but in Et_2O solvent (expts. 11-14) the yields were considerably lower (42-61%).

The reactions of 1-chlorodecane (expts. 15-21) illustrate the superiority of $Li_2Cu(CH_3)_3$ over $LiCu(CH_3)_3$ in THF or Et_2O in the substitution of methyl for chlorine. In THF, a quantitative yield was obtained with $Li_2Cu(CH_3)_3$, whereas with $LiCu(CH_3)_2$ only 22% yield was observed and in the case of CH_3Li in THF, practically no reaction at all was observed under the same conditions. Although yields are low in all other cases studied involving reaction of the new cuprates and CH_3Li with 1-fluorodecane, a quantitative yield of n-undecane was observed when $Li_2Cu(CH_3)_3$ in ether was the reagent. It is interesting to note that wheras $Li_2Cu(CH_3)_3$ in THF is a superior reagent for chlorine displacement, the same reagent in Et_2O is superior for fluorine displacement (expts. 22-28).

The reactions of 6-bromo-1-hexene and 6-chloro-1-hexene behaved similarly to 1-bromodecane and 1-chlorodecane (expts. 29-40). In general, THF solvent is more suitable than Et_2O for organocuprate substitution reactions of alkyliodides, bromides and chlorides and the relative reactivities of the cuprates are $Li_2Cu(CH_3)_3 > LiCu(CH_3)_2$, $LiCu_2(CH_3)_3$ and $Li_2Cu_3(CH_3)_5$; although $Li_2Cu(CH_3)_3$ in Et_2O was superior to THF in its reaction with 1-fluorodecane (expt. 26, 96%). In spite of the fact that CH_3Li produced good yields of substitution products with the iodides and bromides, no reaction took place between CH_3Li and the chlorides and fluorides. In most cases the yield of substitution products is better using the new cuprate $Li_2Cu(CH_3)_3$ than $LiCu(CH_3)_2$ and in many cases the difference in yield is substantial.

The reactions of iodocyclohexane (expts. 41-47) are much slower than the reactions observed earlier with the primary alkyl iodides and in addition considerable metal-halogen interchange is observed. Once again the best substitution reaction was achieved in the reaction of iodocyclohexane with $Li_2Cu(CH_3)_3$ in THF (93% yield with 5% cyclohexane by-product). Reaction of iodocyclohexane with other cuprates and CH_3Li produced substantial amounts of the metal-halogen interchange product, cyclohexane. Under the best conditions, bromocyclohexane (expts. 48-53) gave only 12% yield in its reaction with $Li_2Cu(CH_3)_3$ whereas chlorocyclohexane (expts. 54-58) showed no reaction with any of the reagents after 48 hours. The halogen reactivity decreased in the order I>Br>Cl which is the same trend observed for primary halides.

Experiments 59-82 describe the results of the reaction of various cuprates with the halogenobenzenes in ether and THF. The substitution reactions of iodobenzene can be effected in good yields by each organocuprate studied or methyllithium itself. In the case of bromobenzene, both CH_3Li in ether and $Li_2Cu(CH_3)_3$ in THF caused quantitative substitution whereas the other cuprates were much less effective. The results involving chlorobenzene and fluorobenzene show moderate yields when $LiCu(CH_3)_2$, $Li_2Cu(CH_3)_3$ in THF and $Li_2Cu(CH_3)_3$ in Et_2O are allowed to react. In each case, CH_3Li gives significantly lower yields. Although it was not possible to determine the relative rate of reaction between $Li_2Cu(CH_3)_3$ and $LiCu(CH_3)_2$ in order to see if CH_3Li affects the substitution reactions as well as $LiCu(CH_3)_2$, the reactions of fluorobenzene, *p*-chloroanisole and *p*-fluoroanisole (expts. 83-94) show that $Li_2Cu(CH_3)_3$ is more reactive than $LiCu(CH_3)_2$ in THF or Et_2O in these aryl halide substitution reactions. It is interesting in the case of *p*-chloroanisole only $Li_2Cu(CH_3)_3$ and CH_3Li in ether produced any product at all and that in very modest yield, whereas *p*-fluoroanisole, when allowed to react with $Li_2Cu(CH_3)_3$ in ether, formed *p*-methylanisole in quantititative yield.

It is important to note that $Li_2Cu(CH_3)_3$ in Et_2O reacted with 1-chlorocyclohexene to yield 71% 1-methylcyclohexene whereas all other reagents had no effect on this alkenyl halide (expts. 95-100). When the chlorine atom was placed in the allylic position (3-chlorocyclohexene), $Li_2Cu(CH_3)_3$ in THF had a significantly higher reactivity than the other cuprates (expts. 101-106).

(III-3) Concerning the Reaction of Organocuprates with 4-*tert*-Butylcyclohexanone

Recently, it was reported that a mixture of CH_3Li and $LiCu(CH_3)_2$ provides unusually high stereoselectivity (94% equatorial attack) in the methylation of 4-*tert*-butylcyclohexanone compared to reaction of CH_3Li or $LiCu(CH_3)_2$ alone.[3] It was suggested that "a bulky, highly reactive cuprate having the stoichiometry $Li_2Cu(CH_3)_3$ or $Li_3Cu(CH_3)_4$" was formed when CH_3Li and $LiCu(CH_3)_2$ are allowed to react; and, reaction of these cuprates with the ketone would explain the observed results. However, molecular weight measurements indicate that $Li_2Cu(CH_3)_3$ is monomeric in diethyl ether and THF, whereas CH_3Li is tetrameric and $LiCu(CH_3)_2$ is dimeric. As a monomer, $Li_2Cu(CH_3)_3$ should not be considered more bulky than a tetrametric molecule such as CH_3Li. Reactions of $Li_2Cu(CH_3)_3$, $LiCu(CH_3)_2$ and $LiCu_2(CH_3)_3$ in both diethyl ether and THF with selected enones indicates that $Li_2Cu(CH_3)_3$ is only slightly more reactive than $LiCu(CH_3)_2$ toward conjugate addition. Therefore, the hypothesis that $Li_2Cu(CH_3)_3$, when present in a mixture of CH_3Li and $LiCu(CH_3)_2$ in diethyl ether, is a "bulky, highly reactive cuprate" is questionable.

The CH_3Li-$LiCu(CH_3)_2$ 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: $LiCu(CH_3)_2$, 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 $LiCu(CH_3)_2$ to form a complex which then reacts with the ketone;[3] (2) CH_3Li reacts with LiI to form a complex (a reaction known to produce $Li_4(CH_3)_3I$[9]) which then reacts with the ketone; (3) $LiCu(CH_3)_2$ 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 evidence was reported for the existence of $Li_2Cu(CH_3)_3$ in a mixture of CH_3Li and $LiCu(CH_3)_2$ in dimethyl ether, tetrahydrofuran and diethyl ether solvents. No evidence was found to indicate the presence of any higher order complexes, such

$$CH_3Li + LiCu(CH_3)_2 \rightleftharpoons Li_2Cu(CH_3)_3$$

as $Li_3Cu(CH_3)_4$. The reaction CH_3Li-$LiCu(CH_3)_2$ with 4-tert-butylcyclohexanone in THF did not yield any increased stereoselectivity when compared to CH_3Li alone (Table 11). Since we have determined that

$Li_2Cu(CH_3)_3$ exists in both ether and THF and is monomeric in both solvents, it is doubtful that $Li_2Cu(CH_3)_3$ 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 $Li_2Cu(CH_3)_3$ with the ketone.

The stereochemical improvement in the CH_3Li-$LiCu(CH_3)_2$ 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 CH_3Li-$LiCu(CH_3)_2$ 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[10] and LiBr[11] in THF. Likewise, the stereochemical improvement cannot be explained by assuming that a complex between either $LiCu(CH_3)_2$ or $Li_2Cu(CH_3)_3$ and LiI is reacting with the ketone, since a halide free mixture of CH_3Li and $LiCu(CH_3)_2$ (Table 11) gives the same high stereoselectivity.

The only possibility remaining is that CH_3Li reacts with a complex between one of the components of the mixture and the ketone. This would explain the results in THF, since the ketone would not be expected to compete effectively with THF solvent molecules for coordination sites. This suggestion also explains the unusual rate enhancement in diethyl ether since the concentration of ketone complexed to $LiCu(CH_3)_2$, LiI, etc. would be considerably higher than in THF and certainly the complexed carbonyl compound would be much more reactive than uncomplexed carbonyl.

In order to test this possibility, a system which would be composed of CH_3Li and a lithium salt, was chosen where there would be little chance for complex formation between CH_3Li and the lithium salt but a good chance for complex formation between the lithium salt and the ketone. Such a system would be CH_3Li and $LiClO_4$, since $LiClO_4$ is known to complex the carbonyl group of ketones. Low temperature ^1H and ^{13}C NMR of CH_3Li-$LiClO_4$ mixtures show only signals for pure CH_3Li indicating the absence of any complex formation. ^{13}C NMR of 4-tert-butylcyclohexanone mixtures with LiBr, LiI and $LiClO_4$ in diethyl ether show a downfield shift for the carbonyl carbon of about 10 ppm, indicating the presence of a complex (Table 12). In THF, only a small downfield shift was observed with $LiClO_4$ indicating the presence of very little complexed ketone. The reaction of the CH_3Li-$LiClO_4$ mixture with 4-tert-butylcyclohexanone in diethyl ether (Table 11) shows the same stereochemical improvement as was obtained with CH_3Li-$LiCu(CH_3)_2$. In THF, this reaction (Table 11) showed no improvement in stereoselectivity over that obtained with CH_3Li alone.

The detailed results of stereoselective methylation effected by lithium salts, for example, LiBr, LiI, $LiClO_4$ and $LiCu(CH_3)_2$, are shown in Table 13. Generally, the stereoselectivity is not only dependent on the individual lithium salt but also on the reaction temperature. For example, $LiCu(CH_3)_2$ in conjunction with $LiClO_4$ increases the equatorial attack more than LiI and LiBr, which roughly had the same effect on ^{13}C NMR chemical shift (Table 12). More equatorial attack was observed at -78°C than at higher reaction temperatures. It seems that the molar ratio of methyl lithium to lithium salt is not an important fact for stereoselective methylation except in the case of LiBr. Kinetic studies have shown that the presence of lithium salts increase the reaction rate by 1000. In this case, the lithium salt effect is only a catalytic effect.

CHAPTER IV

CONCLUSIONS

(IV-1)

The new organocuprates, $LiCu_2(CH_3)_3$ and $Li_2Cu(CH_3)_3$ in THF and $Li_2Cu(CH_3)_3$ and $Li_2Cu_3(CH_3)_5$ in Et_2O, react with enones in a similar manner compared to $LiCu(CH_3)_2$. Except in the cases of disubstituted enones, $Li_2Cu(CH_3)_3$ gives quantitative conjugate methylation of the enones studied at a comparable or greater rate than $LiCu(CH_3)_2$ provided the reaction is carried out in THF. On the other hand, poor regioselectivity was observed in diethyl ether. $LiCu_2(CH_3)_3$ gave quantitative regioselectivity in THF and reacted in general more slowly than $LiCu(CH_3)_2$. Since $LiCu_2(CH_3)_3$ is insoluble in diethyl ether, studies were not carried out in this solvent. $Li_2Cu_3(CH_3)_5$ in ether gave excellent results with all the enones and appeared to react somewhat more rapidly compared to $LiCu(CH_3)_2$.

(IV-2)

In general, $Li_2Cu(CH_3)_3$ exhibits a higher reactivity than other cuprates in halide substitution reactions involving alkyl-, cyclo alkyl- and aryl halides. Also, in most cases, $LiCu_2(CH_3)_3$ in THF and $Li_2Cu_3(CH_3)_5$ in Et_2O were considerably less effective than $LiCu(CH_3)_2$ or $Li_2Cu(CH_3)_3$ in the same reactions. Most often THF was the superior solvent although in some cases, ether was decidedly better. The superiority of $Li_2Cu(CH_3)_3$ over $LiCu(CH_3)_3$ and the other cuprates in most cases reported here indicates a potential for this reagent in other reactions not heretofore explored.

(IV-3)

The results shown in Table 13 indicate that CH_3Li-LiBr, CH_3Li-LiI, CH_3Li-$LiClO_4$ and CH_3Li-$LiCu(CH_3)_2$ mixtures react with 4-*tert*-butylcyclohexanone in diethyl ether to give higher stereoselectivity in the product methyl carbionls than were obtained with CH_3Li alone. The results suggest that the methylation reaction is proceeding by attack of CH_3Li on a ketone complex. In the particular case where a CH_3Li-$LiCu(CH_3)_2$ mixture is allowed to react with 4-*tert*-butylcyclohexanone, the results suggest that the methylation is proceeding by CH_3Li attack on a complex between $LiCu(CH_3)_2$ and the ketone.

Table 8. Methylation of Enones with $LiCu(CH_3)_2$, $LiCu_2(CH_3)_3$, and $Li_2Cu(CH_3)_3$[a] in THF at Room Temperature

Exp.	Cuprate Reagent	Enone	Molar Ratio of Reagent to Enone	Reaction Time	Enone Recovered %	Product % 1,4-Methylation	Product % 1,2-Methylation
1	$LiCu(CH_3)_2$	$t\text{-BuCH=CHC(O)Bu}^t$ (trans) (I)	3:1	3 hr	5	95	0
2	$LiCu_2(CH_3)_3$	(I)	3:1	3 hr	20	82	0
3	$Li_2Cu(CH_3)_3$	(I)	2:1	3 hr	0	108	0
4	$LiCu(CH_3)_2$	$CH_3CH{=}CHC(O)CH_3$ (II)	3:1	3 hr	7	93	0
5	$LiCu_2(CH_3)_3$	(II)	3:1	3 hr	11	90	0
6	$Li_2Cu(CH_3)_3$	(II)	2:1	3 hr	11	93	0
7	$LiCu(CH_3)_2$	$CH_3CH{=}C(CH_3)-C(O)CH_3$ (III)	3:1	3 hr	44	56	0
8	$LiCu_2(CH_3)_3$	(III)	3:1	3 hr	95	0	0
9	$Li_2Cu(CH_3)_3$	(III)	2:1	3 hr	48	52	0
10	$LiCu(CH_3)_2$	$(CH_3)_2C{=}CHC(O)CH_3$ (IV)	3:1	3 hr	49	51	0

Table 8. (Continued)

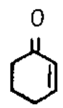
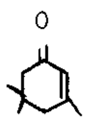
Exp.	Cuprate Reagent	Enone	Molar Ratio of Reagent to Enone	Reaction Time	Enone Recovered %	Product % 1,4-Methylation	1,2-Methylation
11	$LiCu_2(CH_3)_3$	(IV)	3:1	3 hr	66	30	0
12	$Li_2Cu(CH_3)_3$	(IV)	2:1	5 hr	30	8	59
13	$LiCu(CH_3)_2$	 (V)	3:1	3 hr	0	100	0
14	$LiCu_2(CH_3)_3$	(V)	3:1	3 hr	0	103	0
15	$Li_2Cu(CH_3)_3$	(V)	2:1	3 hr	0	95	0
16	$LiCu(CH_3)_2$	 (V)	3:1	5 hr	100	0	0
17	$LiCu_2(CH_3)_3$	(VI)	3:1	5 hr	100	0	0

Table 8. (Continued)

Exp.	Cuprate Reagent	Enone	Molar Ratio of Reagent to Enone	Reaction Time	Recovered %	Product % 1,4-Methylation	1,2-Methylation
18	$Li_2Cu(CH_3)_3$	(VI)	2:1	5 hr	100	0	0

a. $Li_2Cu(CH_3)_3$ is in equilibrium with $LiCu(CH_3)_2$ and CH_3Li.

Table 9. Methylation of Enones with $LiCu(CH_3)_2$ and $Li_2Cu(CH_3)_3$ in Et_2O at Room Temperature

Exp.	Cuprate Reagent	Enone	Molar Ratio of Reagent:Enone	Reaction Time	Enone Recovered %	Product, % 1,4 Methylation	1,2 Methylation
19	$LiCu(CH_3)_2$	I	1:1	10 min	37	63	0
20	$LiCu(CH_3)_2$	I	3:1	10 min	0	100	0
21	$Li_2Cu_3(CH_3)_5$	I	1:1	10 min	0	105	0
22	$Li_2Cu(CH_3)_3$	I	2:3	10 min	0	53	47
23	$LiCu(CH_3)_2$	II	3:1	10 min	3	97	0
24	$Li_2Cu(CH_3)_5$	II	1:1	10 min	0	108	0
25	$Li_2Cu(CH_3)_3$	II	2:1	10 min	0	96	3
26	$LiCu(CH_3)_2$	III	3:1	10 min	6	94	0
27	$Li_2Cu_3(CH_3)_5$	III	1:1	10 min	0	95	0
28	$Li_2Cu(CH_3)_3$	III	2:1	10 min	0.5	14	86
29	$LiCu(CH_3)_2$	IV	3:1	10 min	17	82	1
30	$Li_2Cu_3(CH_3)_5$	IV	1:1	10 min	6	96	0
31	$Li_2Cu(CH_3)_3$	IV	2:1	10 min	2	19	79

Table 9. (Continued)

Exp.	Cuprate Reagent	Enone	Molar Ratio of Reagent:Enone	Reaction Time	Enone Recovered %	Product, % 1,4 Methylation	1,2 Methylation
32	$LiCu(CH_3)_2$	V	1:1	1 min	9	91	0
33	$Li_2Cu_3(CH_3)_5$	V	1:1	10 min	0	95	0
34	$Li_2Cu(CH_3)_3$	V	2:3	1 min	0	100	0
35	$LiCu(CH_3)_2$	VI	3:1	10 min	0	100	0
36	$Li_2Cu_3(CH_3)_5$	VI	1:1	10 min	0	94	0
37	$Li_2Cu(CH_3)_3$	VI	2:1	10 min	0	3	93

Table 10. Substitution Reactions of Halides with $LiCu(CH_3)_2$, $LiCu_2(CH_3)$, $Li_2Cu(CH_3)_3$, $Li_2Cu_3(CH_3)_5$ and CH_3Li at Room Temperature

Exp.	Cuprate Reagent	Halide Substrate	Reaction Time and Solvent	Product(s) and Yield(s) (%)
1	$LiCu(CH_3)_2$	1-Iododecane	10 min, THF 1 hr, THF	*n*-Undecane (57) *n*-Undecane (100)
2	$LiCu_2(CH_3)_3$	1-Iododecane	10 min, THF 1 hr, THF	*n*-Undecane (65) *n*-Undecane (104)
3	$Li_2Cu(CH_3)_3$	1-Iododecane	10 min, THF 1 hr, THF	*n*-Undecane (92) *n*-Undecane (98)
4	$LiCu(CH_3)_2$	1-Iododecane	1 hr, Et_2O	*n*-Undecane (106)
5	$Li_2Cu(CH_3)_3$	1-Iododecane	1 hr, Et_2O 3 hr, Et_2O	*n*-Undecane (76) *n*-Undecane (101)
6	$Li_2Cu_3(CH_3)_5$	1-Iododecane	1 hr, Et_2O	*n*-Undecane (59)
7	CH_3Li	1-Iododecane	1 hr, Et_2O	*n*-Undecane (30) *n*-Decane (50)
8	$LiCu(CH_3)_2$	1-Bromodecane	1 hr, THF	*n*-Undecane (98)
9	$LiCu_2(CH_3)_3$	1-Bromodecane	1 hr, THF	*n*-Undecane (96)
10	$Li_2Cu(CH_3)_3$	1-Bromodecane	1 hr, THF	*n*-Undecane (96)
11	$LiCu(CH_3)_2$	1-Bromodecane	1 hr, Et_2O	*n*-Undecane (42)

Table 10. (Continued)

Exp.	Cuprate Reagent	Halide Substrate	Reaction Time and Solvent	Product(s) and Yield(s) (%)
12	$Li_2Cu(CH_3)_3$	1-Bromodecane	1 hr, Et_2O	n-Undecane (44)
13	$Li_2Cu_3(CH_3)_5$	1-Bromodecane	1 hr, Et_2O	n-Undecane (61)
14	CH_3Li	1-Bromodecane	1 hr, Et_2O	n-Undecane (95)
15	$LiCu(CH_3)_2$	1-Chlorodecane	12 hr, THF	n-Undecane (22)
16	$LiCu_2(CH_3)_3$	1-Chlorodecane	12 hr, THF	n-Undecane (60)
17	$Li_2Cu(CH_3)_3$	1-Chlorodecane	12 hr, THF	n-Undecane (102)
18	$LiCu(CH_3)_2$	1-Chlorodecane	12 hr, Et_2O	n-Undecane (14)
19	$Li_2Cu(CH_3)_3$	1-Chlorodecane	12 hr, Et_2O	n-Undecane (37)
20	$Li_2Cu_3(CH_3)_5$	1-Chlorodecane	12 hr, Et_2O	n-Undecane (30)
21	CH_3Li	1-Chlorodecane	12 hr, Et_2O	n-Undecane (0)
22	$LiCu(CH_3)_2$	1-Fluorodecane	48 hr, THF	n-Undecane (2)
23	$LiCu_2(CH_3)_3$	1-Fluorodecane	48 hr, THF	n-Undecane (2)
24	$Li_2Cu(CH_3)_3$	1-Fluorodecane	48 hr, THF	n-Undecane (8)
25	$LiCu(CH_3)_2$	1-Fluorodecane	24 hr, Et_2O	n-Undecane (24)

Table 10. (Continued)

Exp.	Cuprate Reagent	Halide Substrate	Reaction Time and Solvent	Product(s) and Yield(s) (%)
26	$Li_2Cu(CH_3)_3$	1-Fluorodecane	24 hr, Et_2O	n-Undecane (96)
27	$Li_2Cu_3(CH_3)_5$	1-Fluorodecane	24 hr, Et_2O	n-Undecane (13)
28	CH_3Li	1-Fluorodecane	24 hr, Et_2O	n-Undecane (0)
29	$LiCu(CH_3)_2$	6-Bromo-1-hexene	1 hr, THF	1-heptene (95)
30	$LiCu_2(CH_3)_3$	6-Bromo-1-hexene	1 hr, THF	1-heptene (105)
31	$Li_2Cu(CH_3)_3$	6-Bromo-1-hexene	1 hr, THF	1-heptene (108)
32	$LiCu(CH_3)_2$	6-Bromo-1-hexene	3 hr, Et_2O	1-heptene (88)
33	$Li_2Cu(CH_3)_3$	6-Bromo-1-hexene	3 hr, Et_2O	1-heptene (86)
34	CH_3Li	6-Bromo-1-hexene	1 hr, THF	1-heptene (93)
35	$LiCu(CH_3)_2$	6-Chloro-1-hexene	24 hr, THF	1-heptene (84)
36	$LiCu_2(CH_3)_3$	6-Chloro-1-hexene	24 hr, THF	1-heptene (75)
37	$Li_2Cu(CH_3)_3$	6-Chloro-1-hexene	24 hr, THF	1-heptene (95)
38	$LiCu(CH_3)_2$	6-Chloro-1-hexene	24 hr, Et_2O	1-heptene (68)
39	$Li_2Cu(CH_3)_3$	6-Chloro-1-hexene	24 hr, Et_2O	1-heptene (92)

Table 10. (Continued)

Exp.	Cuprate Reagent	Halide Substrate	Reaction Time and Solvent	Product(s) and Yield(s) (%)	
40	CH_3Li	6-Chloro-1-hexene	24 hr, Et_2O	1-heptene (0)	
41	$LiCu(CH_3)_2$	Iodocyclohexane	48 hr, THF	Methylcyclohexane (21)	Cyclohexane (14)
42	$LiCu_2(CH_3)_3$	Iodocyclohexane	48 hr, THF	Methylcyclohexane (5)	Cyclohexane (15)
43	$Li_2Cu(CH_3)_3$	Iodocyclohexane	48 hr, THF	Methylcyclohexane (93)	Cyclohexane (5)
44	$LiCu(CH_3)_2$	Iodocyclohexane	48 hr, Et_2O	Methylcyclohexane (68)	Cyclohexane (20)
45	$Li_2Cu(CH_3)_3$	Iodocyclohexane	48 hr, Et_2O	Methylcyclohexane (53)	Cyclohexane (32)
46	CH_3Li	Iodocyclohexane	5 hr, Et_2O	Methylcyclohexane (0)	Cyclohexane (97)
47	CH_3Li	Iodocyclohexane	48 hr, THF	Methylcyclohexane (26)	Cyclohexane (10)
48	$LiCu(CH_3)_2$	Bromocyclohexane	48 hr, THF	Methylcyclohexane (0)	Cyclohexane (0)
49	$LiCu_2(CH_3)_3$	Bromocyclohexane	48 hr, THF	Methylcyclohexane (3)	Cyclohexane (0)
50	$Li_2Cu(CH_3)_3$	Bromocyclohexane	48 hr, THF	Methylcyclohexane (3)	Cyclohexane (0)
51	$LiCu(CH_3)_2$	Bromocyclohexane	48 hr, Et_2O	Methylcyclohexane (12)	Cyclohexane (0)
52	$Li_2Cu(CH_3)_3$	Bromocyclohexane	48 hr, Et_2O	Methylcyclohexane (12)	Cyclohexane (4)
53	CH_3Li	Bromocyclohexane	48 hr, Et_2O	Methylcyclohexane (0)	Cyclohexane (27)

Table 10. (Continued)

Exp.	Cuprate Reagent	Halide Substrate	Reaction Time and Solvent	Product(s) and Yield(s) (%)	
54	$LiCu(CH_3)_2$	Chlorocyclohexane	48 hr, THF	Methylcyclohexane (0)	Cyclohexane (0)
55	$LiCu_2(CH_3)_3$	Chlorocyclohexane	48 hr, THF	Methylcyclohexane (0)	Cyclohexane (0)
56	$Li_2Cu(CH_3)_3$	Chlorocyclohexane	48 hr, THF	Methylcyclohexane (0)	Cyclohexane (0)
57	$LiCu(CH_3)_2$	Chlorocyclohexane	48 hr, Et_2O	Methylcyclohexane (0)	Cyclohexane (0)
58	$Li_2Cu(CH_3)_3$	Chlorocyclohexane	48 hr, Et_2O	Methylcyclohexane (0)	Cyclohexane (0)
59	$LiCu(CH_3)_2$	Iodobenzene	14 hr, THF	Toluene (91)	
60	$LiCu_2(CH_3)_3$	Iodobenzene	14 hr, THF	Toluene (91)	
61	$Li_2Cu(CH_3)_3$	Iodobenzene	14 hr, THF	Toluene (96)	
62	$LiCu(CH_3)_2$	Iodobenzene	14 hr, Et_2O	Toluene (82)	
63	$Li_2Cu(CH_3)_3$	Iodobenzene	14 hr, Et_2O	Toluene (92)	
64	CH_3Li	Iodobenzene	14 hr, Et_2O	Toluene (95)	
65	$LiCu(CH_3)_2$	Bromobenzene	24 hr, THF	Toluene (45)	
66	$LiCu_2(CH_3)_3$	Bromobenzene	24 hr, THF	Toluene (0)	
67	$Li_2Cu(CH_3)_3$	Bromobenzene	24 hr, THF	Toluene (102)	

Table 10. (Continued)

Exp.	Cuprate Reagent	Halide Substrate	Reaction Time and Solvent	Product(s) and Yield(s) (%)
68	$LiCu(CH_3)_2$	Bromobenzene	24 hr, Et_2O	Toluene (59)
69	$Li_2Cu(CH_3)_3$	Bromobenzene	24 hr, Et_2O	Toluene (61)
70	CH_3Li	Bromobenzene	24 hr, Et_2O	Toluene (115)
71	$LiCu(CH_3)_2$	Chlorobenzene	24 hr, THF	Toluene (65)
72	$LiCu_2(CH_3)_3$	Chlorobenzene	24 hr, THF	Toluene (0)
73	$Li_2Cu(CH_3)_3$	Chlorobenzene	24 hr, THF	Toluene (42)
74	$LiCu(CH_3)_2$	Chlorobenzene	24 hr, Et_2O	Toluene (0)
75	$Li_2Cu(CH_3)_3$	Chlorobenzene	24 hr, Et_2O	Toluene (47)
76	CH_3Li	Chlorobenzene	24 hr, Et_2O	Toluene (33)
77	$LiCu(CH_3)_2$	Fluorobenzene	24 hr, THF	Toluene (24)
78	$LiCu_2(CH_3)_3$	Fluorobenzene	24 hr, THF	Toluene (0)
79	$Li_2Cu(CH_3)_3$	Fluorobenzene	24 hr, THF	Toluene (49)
80	$LiCu(CH_3)_2$	Fluorobenzene	24 hr, Et_2O	Toluene (0)
81	$Li_2Cu(CH_3)_3$	Fluorobenzene	24 hr, Et_2O	Toluene (50)

Table 10. (Continued)

Exp.	Cuprate Reagent	Halide Substrate	Reaction Time and Solvent	Product(s) and Yield(s) (%)
82	CH_3Li	Fluorobenzene	24 hr, THF	Toluene (21)
83	$LiCu(CH_3)_2$	p-Chloroanisole	48 hr, THF	p-Methylanisole (0)
84	$LiCu_2(CH_3)_3$	p-Chloroanisole	48 hr, THF	p-Methylanisole (0)
85	$Li_2Cu(CH_3)_3$	p-Chloroanisole	48 hr, THF	p-Methylanisole (0)
86	$LiCu(CH_3)_2$	p-Chloroanisole	48 hr, Et_2O	p-Methylanisole (0)
87	$Li_2Cu(CH_3)_3$	p-Chloroanisole	48 hr, Et_2O	p-Methylanisole (21)
88	CH_3Li	p-Chloroanisole	48 hr, Et_2O	p-Methylanisole (11) Anisole (8)
89	$LiCu(CH_3)_2$	p-Fluoroanisole	48 hr, THF	p-Methylanisole (0)
90	$LiCu_2(CH_3)_3$	p-Fluoroanisole	48 hr, THF	p-Methylanisole (0)
91	$Li_2Cu(CH_3)_3$	p-Fluoroanisole	48 hr, THF	p-Methylanisole (83)
92	$LiCu(CH_3)_2$	p-Fluoroanisole	48 hr, Et_2O	p-Methylanisole (3)
93	$Li_2Cu(CH_3)_3$	p-Fluoroanisole	48 hr, Et_2O	p-Methylanisole (101)
94	CH_3Li	p-Fluoroanisole	48 hr, Et_2O	p-Methylanisole (82)

Table 10. (Continued)

Exp.	Cuprate Reagent	Halide Substrate	Reaction Time and Solvent	Product(s) and Yield(s) (%)
95	$LiCu(CH_3)_2$	1-Chlorocyclohexene	48 hr, THF	1-methylcyclohexene (0)
96	$LiCu_2(CH_3)_3$	1-Chlorocyclohexene	48 hr, THF	1-methylcyclohexene (0)
97	$Li_2Cu(CH_3)_3$	1-Chlorocyclohexene	48 hr, THF	1-methylcyclohexene (0)
98	$LiCu(CH_3)_2$	1-Chlorocyclohexene	48 hr, Et_2O	1-methylcyclohexene (0)
99	$Li_2Cu(CH_3)_3$	1-Chlorocyclohexene	48 hr, Et_2O	1-methylcyclohexene (71)
100	CH_3Li	1-Chlorocyclohexene	48 hr, Et_2O	1-methylcyclohexene (0)
101	$LiCu(CH_3)_2$	3-Chlorocyclohexene	48 hr, THF	3-Methylcyclohexene (57)
102	$LiCu_2(CH_3)_3$	3-Chlorocyclohexene	48 hr, THF	3-Methylcyclohexene (33)
103	$Li_2Cu(CH_3)_3$	3-Chlorocyclohexene	48 hr, THF	3-Methylcyclohexene (83)
104	$LiCu(CH_3)_2$	3-Chlorocyclohexene	48 hr, Et_2O	3-Methylcyclohexene (58)
105	$Li_2Cu(CH_3)_3$	3-Chlorocyclohexene	48 hr, Et_2O	3-Methylcyclohexene (62)
106	CH_3Li	3-Chlorocyclohexene	48 hr, Et_2O	3-Methylcyclohexene (8)

Table 11. Reactions of Organometallic Reagents with 4-*tert*-Butylcyclohexanone in Ether Solvents at -78°

Reagent	Yield of Axial Alcohol Ether	THF
CH_3Li	69	65
$2CH_3Li + LiCu(CH_3)_2$	92	65
$2CH_3Li + LiCu(CH_3)_2$ (halide free)	93	65
$CH_3Li + LiBr$	87	65
$CH_3Li + LiI$	87	65
$CH_3Li + LiClO_4$	92	67

Table 12. ^{13}C NMR Chemical Shift (from TMS) of Carbonyl Carbon of 4-*tert*-Butylcyclohexanone with Lithium Salts

ppm	Δppm	lithium salt (solvent)
206.9	0	none (Et_2O)
209.4	2.5	1 mole equivalent of LiBr (Et_2O)
209.9	3.0	2 mole equivalent of LiBr (Et_2O)
217.3	10.4	1 mole equivalent of LiI (Et_2O)
217.6	11.7	2 mole equivalent of LiI (Et_2O)
217.0	10.1	1 mole equivalent of $LiClO_4$ (Et_2O)
218.3	11.4	2 mole equivalent of $LiClO_4$ (Et_2O)
218.4	11.5	1 mole equivalent of $LiCu(CH_3)_2$-halide free (Et_2O)
207.9	0	none (THF)
209.3	2.4	1 mole equivalent of $LiClO_4$(THF)

Table 13. Reactions of CH_3Li-Lithium Salts with 4-*tert*-Butylcyclohexanone and 2-Methycyclohexanone in Et_2O Solvent for 1 Hour

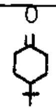
Exp.	CH_3Li	LiI	LiBr		Condition	Ketone Recovered	Ax-OH	Eq-OH
1	2	0	0	1	dry ice temp.	0	70	30
2	3	1	0	1.5	dry ice temp.	0	81	19
3	3	0	1	1.5	dry ice temp.	0	76	24
4	2	0	1	1	dry ice temp.	0	78.5	21.5
5	2	0	0	1	-78°C	0	69	31
6	3	1	0	1.5	-78°C	0	87	13
7	3	2	0	1.5	-78°C	0	87	13
8	1	3	0	0.5	-78°C	0	87	13
9	2	3	0	1	-78°C	0	86	14
10	3	2	3	1.5	-78°C	0	86	14
11	3	0	1	1.5	-78°C	0	80	20

Table 13. (Continued)

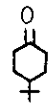
Exp.	CH_3Li	LiI	LiBr		Condition	Ketone Recovered	Ax-OH	Eq-OH
12	3	0	2	1.5	-78°C	0	82	18
13	3	0	3	1.5	-78°C	0	87	13
14	3	0	9	1.5	-78°C	0	86	14
		$LiClO_4$						
15	1	1		0.5	-78°C	0	92	8
16	1	2		0.5	-78°C	0	91	9
		CuI	LiBr					
17	6	3	0	1	-78°C	100	0	0
18	6	3	6	1	-78°C	100	0	0
19	8	3	0	1	-78°C	0	93	7
20	8	3	8	1	-78°C	0	93	7
21	9	3	0	1	-78°C	0	93	7
22	4	1	0	1	-78°C	0	94	6

Table 13. (Continued)

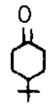
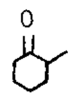
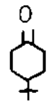
Exp.	CH_3Li			Condition	Ketone Recovered	Ax-OH	Eq-OH
		$LiCu(CH_3)_2$(LiI free)					
23	2	1	1	-78°C	1(0)	89 (90)	11 (10)
24	3	1	1.5	-78°C	0	93	7
25	1	3	0.5	-78°C	0	92	8
30	1	1	0.5	-78°C	0	92	8
		LiI					
26	1	1	0.5	-78°C	0	97.5	2.5
		$LiClO_4$					
27	1	1	0.5	-78°C	0	98	2
		LiBr					
28	1	1	0.5	-78°C	0	97	3
29	1		0.5	-78°C	0	94	6

Table 13. (Continued)

Exp.	CH_3Li	LiI		Condition	Ketone Recovered	Ax-OH	Eq-OH
30	1	1	0.33	-78° 10 sec	0	88	12
				60 sec	0	88	12
		$LiCu(CH_3)_2$ (LiI free)					
31	1	1	0.33	-78° 10 sec	0	92	8
				60 sec	0	92	8
				30 min	0	93	7

32	1		0.33	-78° 1 min	56	70	30
				3 min	45	70	30
				5 min	36	70	30
				15 min	15	70	30
				30 min	6	70	30
				60 min	0	70	30

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PART III

APPLICATION OF COMPLEX METAL HYDRIDES OF COPPER IN ORGANIC REACTIONS

CHAPTER I

INTRODUCTION

Background

The application of copper hydride reagents in organic synthesis has been a topic of great interest in the past ten years. Recently, LiCuHR compounds (where R=1-pentyne, O-t-Bu, and SPh) have been prepared and used as selective reducing reagents in order to effect conjugate reduction of α,β-unsaturated carbonyl compounds.[1] Almost at the same time, LiCuHR compounds (where R=alkyl and alkynyl) were evaluated as reagents for the selective removal of halo and mesyloxyl groups from RX compounds as well as for the reduction of α,β-unsaturated ketones.[2] More recently, the mixture obtained by the combination of $2LiAlH(OCH_3)_3$ with CuBr or of $NaAlH_2(OCH_2CH_2OCH_3)_2$ with CuBr has been demonstrated to possess the ability to reduce conjugated carbonyl compounds to the corresponding saturated derivatives. The intermediates in these reagents were speculated to be "complex copper hydrides," although no evidence was presented to establish this point.[3] Dilts and Shriver[4] have prepared a stable solution of CuH in pyridine and suggested that the solubility of CuH is due to its complexation with pyridine. Stable complexes of CuH with PPh_3 have also been prepared by Churchill and co-workers.[5] Uncomplexed CuH is known to be quite unstable even at temperatures as low as -80°C. Monnier has claimed the preparation of $CuAlH_4$; however, it is reported to be unstable above -80°C and decomposes to Cu, CuH, Al and

H_2.[6] Ashby has recently reported the formation of $CuAlH_4$ and Cu_3AlH_6 as intermediates in the reaction of $LiAlH_4$ and CuI at low temperature.[7] Also recently, Ashby prepared the first stable complex metal hydride of copper, $LiCuH_2$, by the reaction of $LiAlH_4$ with lithium dimethylcuprate and found the product to be stable to 70°C.[8]

More recently, the existence of some new organocuprates has been established by variable temperature NMR, namely $LiCu_2(CH_3)_3$ and $Li_2Cu(CH_3)_3$[9] and it has been shown that these new cuprates behave differently from $LiCu(CH_3)_2$ towards enones[10] and organohalides.[11] In continuation of present investigations in the field of copper chemistry, we have recently been able to prepare a series of complex metal hydrides of copper, $Li_nCu_mH_{(n+m)}$ (where n=1-5 and m=1-2) which are not only stable at room temperature (except for $LiCu_2H_3$), but also some of which are soluble in THF ($LiCuH_2$ and Li_4CuH_5). These hydrides are pure compounds and not mixtures, according to x-ray and DTA-TGA data[12] as well as evidence that appears in this study.

Purpose

The purpose of these studies is to investigate the reactions of the new complex metal hydrides of copper with alkyl halides, enones, and cyclic ketones in order to explore their reactivity, regioselectivity, and stereoselectivity.

CHAPTER II

EXPERIMENTAL

Note: Preparation of the complex metal hydrides of copper used in these studies was carried out by co-worker, Dr. A. B. Goel.[12]

General Considerations

Techniques for handling air-sensitive compounds, apparatus, and instruments used are the same as previously described in the experimental sections of Part I and Part II.

Materials

The sources and methods for the purifications of tetrahydrofuran, diethyl ether, cuprous iodide, methyl lithium, lithium aluminum hydride solution, 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one, 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, and 2-methylcyclohexanone have been described in Parts I and II.

Halide substrates and authentic samples of products were purchased commercially and used without further purification: iodo-, bromo-, chloro- and fluorodecane (Eastman Organic Chemicals), cyclohexyl chloride (Aldrich Chemical Company), 1-chlorocyclohexene and 3-chlorocyclohexene (Friton Laboratories).

n-Octyl tosylate was prepared by reaction of *n*-octanol (7 g, ca. 0.05 M) in pyridine (16g) with *p*-toluenesulfonyl chloride (10.5 g, ca. 0.055 M) at 20°C overnight. The work-up was by HCl-ice water hydrolysis followed by benzene extraction. The pure product was obtained by distillation, b.p. 155-6°C/2mm/Hg, NMR ($CDCl_3$) δ7.66 (2H,d) 7.25 (2H,d), 3.94 (2H,t, CH_2-O), 2.40 (3H, s, benzyl CH_3), 2.0-0.8 (15H, m, alkyl).

Preparation of $Li_nCuH_{(n+1)}$ by the Reaction of $Li_nCu(CH_3)_{n+1}$ with $(\frac{n+1}{2})$ $LiAlH_4$ in Diethyl Ether

To a well-stirred slurry of cuprous iodide in diethyl ether at -78°C was added dropwise CH_3Li in diethyl ether in various ratios (CH_3Li:CuI = 2:1, 3:1, 4:1, 5:1 or 6:1). A clear solution resulted in every case within a few minutes. These reaction mixtures were stirred at -78°C for 1/2 hour. To these solutions was then added $LiAlH_4$ dropwise with stirring [$Li_nCu(CH_3)_{n+1}$:$LiAlH_4$ = (n+1):$(\frac{n+1}{2})$]. No precipitation was observed at -78°; however, a white crystalline solid formed in every case when the reaction mixture was allowed to warm to room temperature. These reaction mixtures were stirred at room temperature for 1 hour and the solids were centrifuged, separated, washed with fresh diethyl ether and a slurry made in ether as well as in THF ($LiCuH_2$ and Li_4CuH_5 dissolved in THF immediately). The products were analyzed before reacting with organic substrates. The supernatant solutions in all cases showed γAl-H stretching at 1710 cm^{-1} [characteristic of $LiAlH_2(CH_3)_2$].

Reactions of Alkyl Halides, n-Octyl Tosylate, Enone I and Cyclic Ketones with Li_nCuH_{n+1}

A 10 ml Erlenmeyer flask with a Teflon coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen flush, then sealed with a rubber septum and connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil bubbler. One ml

THF or Et_2O solvent was introduced into the reaction vessel; then reactant, e.g., halide substrate (0.5 ml, 0.25 M in THF or Et_2O) with internal standard, was syringed into the vessel. Finally, the calculated amount of the hydride, Li_nCuH_{n+1}, in THF or Et_2O was added. After the designated reaction time, the reaction mixture was quenched with a minimum of distilled water and the resulting solution dried over $MgSO_4$. A 20 ft. 8% Apiezon L on Chromosorb W was used to separate the products of decyl halides (120°C, internal standard n-$C_{12}H_{26}$) and n-octyl tosylate (95°C, internal standard n-$C_{10}H_{22}$).

A 10 ft. 5% Carbowax 20M was used to separate the products of 2,2,6,6-tetrametyl-trans-4-hepten-3-one (as described in Part I), 4-tert-butylcyclohexanone (135°C, retention time: 5.6 min. for internal standard, n-$C_{14}H_{30}$; 14.9 min. for ketone, 17.8 min. for axial-alcohol, and 21.3 min. for equatorial alcohol), 3,3,5-trimethylcyclohexanone (150°C, retention time: 5.8 min. for ketone, 7.6 min. for axial-alcohol, 8.7 min. for equatorial-alcohol and 12.5 min. for internal standard, n-$C_{16}H_{34}$). A 15 ft. 10% Diglycerol on Diatoport S was used to separate the product of 2-methylcyclohexanone (90°C, retention time: 3.4 min. for ketone, 5.1 min. for axial-alcohol, 6.1 min. for equatorial alcohol, and 11.7 min. for internal standard n-$C_{14}H_{30}$).

CHAPTER III

RESULTS AND DISCUSSION

When CH_3Li in diethyl ether was added dropwise to a well-stirred slurry of CuI in diethyl ether at -78°C, a clear and colorless solution resulted when the CH_3Li:CuI ratio was 2:1. When $LiAlH_4$ in Et_2O was added to this solution, no precipitate was observed at -78°C; however, when the reaction mixture was allowed to warm to room temperature, a white crystalline solid precipitated. The insoluble solid was filtered, dried, and characterized by elemental analysis and found to be a complex metal hydride of copper. In this way, a series of complex metal hydrides of copper of composition $Li_nCuH_{(n+1)}$ (where n=1 to 5) were prepared by the reaction of $LiAlH_4$ with the corresponding lithium methylcuprates [Equations (1) and (2)].

$$(n+1)CH_3Li + CuI \xrightarrow[-78°]{Et_2O} Li_nCu(CH_3)_{n+1} + LiI \qquad (1)$$

$$Li_nCu(CH_3)_{n+1} + (\frac{n+1}{2})LiAlH_4 \xrightarrow[-78°]{Et_2O} Li_nCuH_{(n+1)} + (\frac{n+1}{2})LiAlH_2(CH_3)_2 \qquad (2)$$

Interestingly, $LiCuH_2$ and Li_4CuH_5 were found to be soluble in THF and Li_4CuH_5 was found to be stable in THF at room temperature. All of the complex metal hydrides of copper, except $LiCu_2H_3$ were found to be stable at room temperature in the solid state or as a slurry in diethyl ether. The thermal stability of these compounds is in the order: $Li_5CuH_6 > Li_4CuH_5 > Li_3CuH_4 > Li_2CuH_3 > LiCuH_2 > LiCu_2H_3$.

The hydride, Li_5CuH_6, is stable to 140°C under vacuum and is stable at room temperature for over a month. Elemental analysis, solubility, and thermal stabilities of these complexes are given in Table 14.

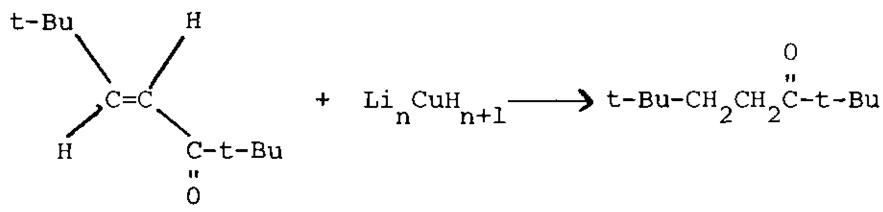
In order to study the reactions of these hydrides with various organic substrates, either a diethyl ether slurry or a THF solution of the hydrides of known concentration were prepared and added to the organic substrates in either diethyl ether or THF.

Reactions of Organohalides and Tosylates

Decyl halides (X=I, Br, Cl and F) and _n_-octyl tosylate were allowed to react with each of the stable complex metal hydrides of copper (i.e., $LiCuH_2$, Li_2CuH_3, Li_3CuH_4, Li_4CuH_5 and Li_5CuH_6). In preliminary experiments, both THF and diethyl ether were evaluated as solvents with the results indicating that THF is the better solvent. For example, the reaction of Li_2CuH_3 with 1-iododecane produced 100% _n_-decane in THF within one hour reaction time at room temperature, but only 72% _n_-decane was formed in diethyl ether solvent in a comparable experiment over the same period of time. A further difference in the two solvents was indicated in close observations of the reactions of 1-iododecane with Li_2CuH_3. In THF, precipitation of a black solid (Cu°) took place immediately when the reagent and substrate were mixed at 22°C, whereas in diethyl ether the black solid formed more slowly. The results of these studies are summarized in Table 15. Each of the five complex metal hydrides of copper react with 1-iododecane to give 100% _n_-decane. The reactivity of substrate to hydride reagent has been found to decrease in the order of I>Br>OTs>Cl>F. For example, reactions of $LiCuH_2$ in THF with 1-iododecane, 1-bromodecane, _n_-octyl tosylate, 1-chlorodecane, and 1-fluorodecane produced products in 100, 85, 64, 37 and 0% yield, respectively. This order was followed throughout for the five hydride reagents, except for a small deviation involving Li_5CuH_6. Li_4CuH_5 was found to be the most reactive hydride, presumably because of its solubility in THF. This hydride reacted with 1-iododecane, 1-bromodecane, 1-chlorodecane, and *n*-octyl tosylate to give quantitative yields of the reduction product in each case. Only ten percent reaction was observed between Li_4CuH_5 and 1-fluorodecane after 24 hours at room temperature (with the reagent still active after the 24-hour reaction period); however, the other hydrides did not react al all with 1-fluorodecane. Reactions involving Li_2CuH_3 and Li_4CuH_5 were also carried out with other chlorides, namely, cyclohexyl chloride, 1-chlorocyclohexene, 3-chlorocyclohexene, and chlorobenzene; only in the case of the reaction of Li_4CuH_5 with 3-chlorocyclohexene was any reaction observed (10%).

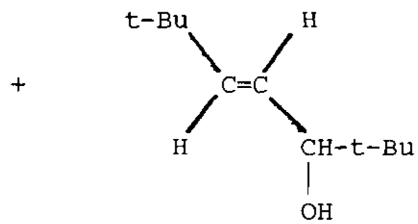
Reactions of 2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one (Enone I)

Enone I was chosen as a representative enone for this study. It has been reported that Enone I can be reduced quantitatively to the 1,2-reduction product (III) by $LiAlH_4$ or to the 1,4-reduction product (II) by H_2AlI. It has also been shown that reaction in THF results in better regioselectivity than in Et_2O solvent.[13] Reactions of each hydride, Li_nCuH_{n+1}, were carried out in THF and Et_2O solvent at room temperature in order to compare the regioselectivity in each solvent. The results are shown in Table 16.



(1,4-reduction product)

(I) (II)



(1,2-reduction product)

(III)

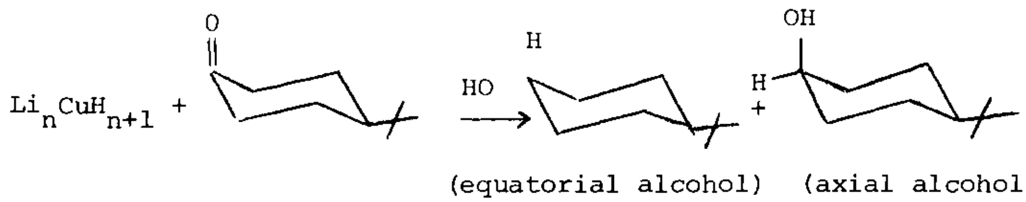
(3)

A comparison of hydride reactivities (i.e., % enone recovered) and regioselectivity (i.e., the distribution of 1,4:1,2-reduction products) demonstrates the characteristic differences of the different hydrides. Li_2CuH_3 and Li_4CuH_5 both have high reactivities, but exhibit entirely different regioselectivities. Li_4CuH_5 behaves very much like $LiAlH_4$, whereas Li_2CuH_3 produces the exact opposite regioselectivity behaving as a good conjugate reducing agent. Li_3CuH_4 and Li_5CuH_6 behave very similar to one another both in reactivity and regioselectivity, whereas $LiCuH_2$ behaves very strangely, producing predominant 1,4-reduction in ether (60:20) and predominant 1,2-reduction in THF

(11:85). These data also provide more evidence that these complex metal hydrides of copper are not physical mixtures of each other or combinations of $LiCuH_2$ and LiH since each stoichiometric compound behaves so differently.

Reactions of 4-tert-Butylcyclohexanone, 3,3,5-Trimethylcyclohexanone and 2-Methylcyclohexanone

The stereoselective reduction of cyclohexanones by metal hydrides has been studied intensively in recent years. $LiAlH_4$ is considered to be the least sterically hindered hydride since it produces 90, 76, and 20% axial attack on 4-tert-butylcyclohexanone, 2-methylcyclohexanone, and 3,3,5-trimethylcyclohexanone, respectively. The more sterically bulky hydrides are subject to "steric approach control" in their approach to any particular cyclohexanone; therefore, the amount of equatorial attack can be considered an indication of the effective bulk of the hydride. Results of the hydride reactions with the cyclohexanones are given in Table 17. Reactions of 4-tert-butylcyclohexanone were carried out in both THF and Et_2O solvents. It appears that the hydrides in THF produce more equatorial attack than in Et_2O except in the case of Li_2CuH_3. The hydride, $LiCuH_2$, in THF provided 78% equatorial attack, which is very unusual compared to $LiAlH_4$ (10% equatorial attack), but gave only 18% equatorial attack in ether solvent. This result suggests a higher effective bulk for $LiCuH_2$ in THF as compared to ether. The results show that the amount of axial alcohol increased in the order: $LiCuH_2 > Li_2CuH_3 > Li_3CuH_4 > Li_4CuH_5 > Li_5CuH_6$.



(4)

Reactions of 3,3,5-trimethylcyclohexanone and 2-methylcyclohexanone with $LiCuH_2$ in THF and Et_2O and Li_4CuH_5 and Li_5CuH_6 in only THF have also been carried out. In both cases involving $LiCuH_2$, the solvent affects the selectivity in the same way as seen in 4-tert-butylcyclohexanone, i.e., 98:86% (THF:Et_2O) equatorial attack in the reduction of 3,3,5-trimethylcyclohexanone and 50:42% (THF:Et_2O) equatorial attack in the reduction of 2-methylcyclohexanone. $LiCuH_2$ appears to be more selective (higher effective bulk) than the other complex metal hydrides of copper towards all of the cyclohexanones studied.

We have made a comparison of the reactivity of Li_4CuH_5 to that of the well-known $LiAlH_4$ in order to obtain some idea of the strength of the new complex metal hydrides of copper as reducing agents. It would appear from the results in Tables 16-17 that the complex metal hydrides of copper in general, and specifically Li_4CuH_5, are weaker reducing agents than $LiAlH_4$. However, when Li_4CuH_5 was prepared for these studies, it was prepared in diethyl ether in which it is insoluble. The ether was then removed under vacuum and THF added to make a slurry. However, if the ether was removed only to the stage of producing a mushy, wet solid and THF added to this mixture, all of the solid immediately dissolved. Table 18 shows the results obtained in a comparison of dissolved Li_4CuH_5 with $LiAlH_4$ in THF. As can be seen from the data, particularly a comparison of reductions of decyl chloride, Li_4CuH_5 is a more powerful reducing agent than $LiAlH_4$. It is also noteworthy that the stereochemistry of reduction of 4-*tert*-butylcyclohexanone by Li_4CuH_5 as a slurry (Table 17, expt. 50; 15:85, axial-OH:eq.-OH) compared to Li_4CuH_5 in solution (Table 18, 45:55, axial-OH:eq.-OH) is quite different.

CHAPTER IV

CONCLUSIONS

Results of reactions of new complex metal hydrides of copper with organic substrates demonstrate their individual integrities and unique properties as reducing agents. In the case of alkyl halides, the new copper hydrides are potentially useful reagents for the reduction to alkanes. Li_4CuH_5, which is soluble in THF, appears to be particularly useful. In the case of enones, it appears that either predominant 1,2 or 1,4-reduction can be obtained depending on the specific hydride used, whereas the new hydrides appear to reduce cyclohexanones similarly to $LiAlH_4$ except in some cases where the reduction is not as selective. A comparison of the rate of reduction for one of the complex metal hydrides of copper (Li_4CuH_5) to $LiAlH_4$ in THF shows that Li_4CuH_5 is the more powerful reducing agent than $LiAlH_4$ toward alkyl halides and probably toward the other substrates as well. The reactivity of the hydrides depends to a large extent on the homogeneous or heterogeneous nature of the hydride, the reactivity being considerably greater when the hydride is soluble in the reaction medium.

Table 14. Analyses and Properties of Complex Metal Hydrides of Copper, $Li_nCuH_{(n+1)}$

Compound	Analysis (Ratio) Li:Cu:H	Solubility in THF	Thermal Decomp. (0°C)
$LiCuH_2$	1.07:1.00:2.01	soluble	70, 300, 400
Li_2CuH_3	2.07:1.00:2.95	insoluble	90, 110, 120, 145, 290, 440
Li_3CuH_4	3.05:1.00:3.97	insoluble	110, 120, 140, 308, 410, 450
Li_4CuH_5	3.95:1.00:4.96	soluble	120, 145, 300, 365, 430, 480-above 500
Li_5CuH_6	5.09:1.00:5.95	insoluble	140, 305, 440, 400-above 500

Table 15. Reactions of Complex Metal Hydrides of Copper with Organohalides and Tosylates in THF at Room Temperature for 24 Hours

Exp.	Hydride Reagent[a]	Halide Substrate	Product(s) & Yield(s) (%)
1	$LiCuH_2$	1-iododecane	_n_-decane (100)
2	$LiCuH_2$	1-bromodecane	_n_-decane (85)
3	$LiCuH_2$	1-chlorodecane	_n_-decane (37)
4	$LiCuH_2$	1-fluorodecane	_n_-decane (0)
5	$LiCuH_2$	_n_-octyl tosylate	_n_-octane (64)
6	Li_2CuH_3	1-iododecane	_n_-decane (100)
7	Li_2CuH_3	1-bromodecane	_n_-decane (100)
8	Li_2CuH_3	1-chlorodecane	_n_-decane (35)
9	Li_2CuH_3	1-fluorodecane	_n_-decane (0)
10	Li_2CuH_3	_n_-octyl tosylate	_n_-octane (80)
11	Li_2CuH_3	cyclohexyl chloride	cyclohexane (0)
12	Li_2CuH_3	1-chlorocyclohexene	cyclohexene (0)
13	Li_2CuH_3	3-chlorocyclohexene	cyclohexene (0)
14	Li_2CuH_3	chlorobenzene	benzene (0)

Table 15. (Continued)

Exp.	Hydride Reagent[a]	Halide Substrate	Product(s) & Yield(s) (%)
15	Li_3CuH_4	1-iododecane	_n_-decane (100)
16	Li_3CuH_4	1-bromodecane	_n_-decane (90)
17	Li_3CuH_4	1-chlorodecane	_n_-decane (34)
18	Li_3CuH_4	1-fluorodecane	_n_-decane (0)
19	Li_3CuH_4	_n_-octyl tosylate	_n_-octane (39)
20	Li_4CuH_5	1-iododecane	_n_-decane (100)
21	Li_4CuH_5	1-bromodecane	_n_-decane (100)
22	Li_4CuH_5	1-chlorodecane	_n_-decane (99)
23	Li_4CuH_5	1-fluorodecane	_n_-decane (10)
24	Li_4CuH_5	_n_-octyl tosylate	_n_-decane (99)
25	Li_4CuH_5	cyclohexyl chloride	cyclohexane (0)
26	Li_4CuH_5	1-chlorocyclohexene	cyclohexene (0)
27	Li_4CuH_5	3-chlorocyclohexene	cyclohexene (10)
28	Li_4CuH_5	chlorobenzene	benzene (0)

Table 15. (Continued)

Exp.	Hydride Reagent[a]	Halide Substrate	Product(s) & Yield(s) (%)
29	Li_5CuH_6	1-iododecane	n-decane (100)
30	Li_5CuH_6	1-bromodecane	n-decane (100)
31	Li_5CuH_6	1-chlorodecane	n-decane (80)
32	Li_5CuH_6	1-fluorodecane	n-decane (0)
33	Li_5CuH_6	n-octyl tosylate	n-decane (69)

a. The molar ratio of hydride reagent to substrate is 1:1, except $LiCuH_2$(2:1) ratio.

Table 16. Reactions of Complex Metal Hydrides of Copper with 2,2,6,6-Tetramethyl-trans-4-hepten-3-one at Room Temperature

Exp.	Hydride Reagent	Reaction Condition	Enone Recovered (%)	Products, % 1,4	1,2
34	$LiCuH_2$	Et_2O, 24 h	20	60	20
35	$LiCuH_2$	THF, 24 h	0	11	85
36	Li_2CuH_3	Et_2O, 48 h	0	93	6
37	Li_2CuH_3	THF, 48 h	0	88	12
38	Li_3CuH_4	Et_2O, 48 h	70	5	25
39	Li_3CuH_4	THF, 48 h	50	5	45
40	Li_4CuH_5	Et_2O, 24 h	0	5	90
41	Li_4CuH_5	THF, 24 h	0	5	95
42	Li_5CuH_6	Et_2O, 48 h	58	4	33
43	Li_5CuH_6	THF, 48 h	25	4	71

Table 17. Reactions of Complex Metal Hydrides of Copper with 4-*tert*-Butylcyclohexanone, 3,3,5-Trimethylcyclohexanone and 2-Methylcyclohexanone at Room Temperature

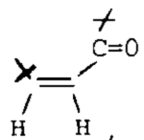
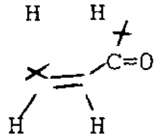
Exp.	Hydride Reagent	Ketone	Reaction Condition	Ketone Recovered	Relative Yield % ax-OH	Relative Yield % eq-OH
44	$LiCuH_2$	4-*tert*-butyl-cyclohexanone	Et_2O, 48 h	0	18	82
45	$LiCuH_2$	4-*tert*-butyl-cyclohexanone	THF, 48 h	0	78	22
46	Li_2CuH_3	4-*tert*-butyl-cyclohexanone	Et_2O, 48 h	17	43	57
47	Li_2CuH_3	4-*tert*-butyl-cyclohexanone	THF, 48 h	20	22	78
48	Li_3CuH_4	4-*tert*-butyl-cyclohexanone	THF, 72 h	0	31	69
49	Li_4CuH_5	4-*tert*-butyl-cyclohexanone	Et_2O, 72 h	16	11	89
50	Li_4CuH_5	4-*tert*-butyl-cyclohexanone	THF, 72 h	40	15	85
51	Li_5CuH_6	4-*tert*-butyl-cyclohexanone	Et_2O, 72 h	50	9	91
52	Li_5CuH_6	4-*tert*-butyl-cyclohexanone	THF, 72 h	55	14	86

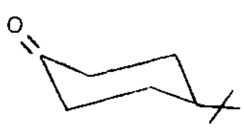
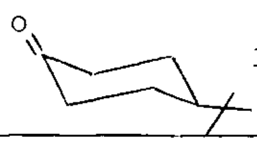
Table 17. (Continued)

Exp.	Hydride Reagent	Ketone	Reaction Condition	Ketone Recovered	Relative Yield % ax-OH	eq-OH
53	$LiCuH_2$	3,3,5-trimethyl-cyclohexanone	Et_2O, 24 h	0	86	14
54	$LiCuH_2$	3,3,5-trimethyl-cyclohexanone	THF, 24 h	0	98	2
55	Li_4CuH_5	3,3,5-trimethyl-cyclohexanone	THF, 24 h	1	82	18
56	Li_5CuH_6	3,3,5-trimethyl-cyclohexanone	THF, 24 h	0	91	9
57	$LiCuH_2$	2-methyl-cyclohexanone	Et_2O, 24 h	0	42	58
58	$LiCuH_2$	2-methyl-cyclohexanone	THF, 24 h	0	50	50
59	Li_4CuH_5	2-methyl-cyclohexanone	THF, 24 h	0	35	65
60	Li_5CuH_6	2-methyl-cyclohexanone	THF, 24 h	0	33	67

Table 18. Comparison of Reactivities of $LiAlH_4$ and Li_4CuH_5 in Equal Molar Ratio in THF at Room Temperature

Hydride	Substrate	Reaction Time	$C_{10}H_{22}$
$LiAlH_4$	C_{10}-I	15 min	98
	C_{10}-Br	15 min	85
		1 h	95
	C_{10}-Cl	15 min	0
		1 h	0
		24 h	68
Li_4CuH_5	C_{10}-I	15 min	100
	C_{10}-Br	15 min	99
	C_{10}-Cl	15 min	0
		1 h	3
		24 h	99

Hydride	Substrate	Reaction Time	enone rec.	1.4	1.2
$LiAlH_4$		15 min	0	0	100
Li_4CuH_5		15 min	0	5	95

Hydride	Substrate	Reaction Time	ketone rec.	ax-OH	eq-OH
$LiAlH_4$		15 min	0	8	92
Li_4CuH_5		15 min	0	45	55

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PART IV

FUNCTIONAL GROUP SELECTIVITY AND STEREOSELECTIVITY INVOLVING MAGNESIUM-HYDROGEN COMPOUNDS

CHAPTER I

INTRODUCTION

Background

In recent years the use of metal hydrides as reducing agents in organic chemistry has attracted considerable attention.[1] Sodium borohydride and lithium aluminum hydride have been known for over twenty years and have been used for the reduction of a number of organic functional groups.[2] However, $LiAlH_4$ has been found to be extremely reactive and in most cases exhibits poor selectivity. Thus, because of the certain deficiencies suffered by most of the common complex metal hydrides, interest in finding new metal hydrides which can function as ideal reducing agents for specific groups has been a continuous effort in organic chemistry.

The stereoselective reduction of cyclic ketones using hydrides of aluminum and boron has been thoroughly studied.[1,3] "Steric approach control" has been considered as one of the most important factors in the explanation of stereochemical results. For example, in the reduction of 4-*tert*-butylcyclohexanone, the hydride with greatest steric bulk, $LiAlH(OCH_3)_3$, yielded the greatest amount of increase of equatorial attack compared to $LiAlH_4$.[4] Recently, lithium trialkylborohydrides have been reported to be very selective reducing agents toward the reduction of cyclic and bicyclic ketones.[3]

Although numerous reports have appeared in the literature concerning the reduction of organic substrates by hydrides of boron and aluminum, nothing is known about the reductive ability of MgH_2, presumably because of its insolubility in all solvents studied.[4] Recently, Ashby and Goel reported the first examples of soluble magnesium-hydrogen compounds in the form of HMgCl, HMgBr[5] and RMgH.[6] Also, for the first time, alkoxy- and dialkylaminomagnesium hydrides were prepared by the reacton of $Mg(OR)_2$ or $Mg(NR_2)_2$ with an active form of MgH_2 in the appropriate stoichiometric ratio in THF at room temperature. The alkoxy- and dialkylaminomagnesium hydrides can be considered as potential reducing agents to effect functional group selectivity and stereoselectivity since most of these compounds exhibit solubility in THF and contain a sterically bulky alkoxy or dialkylamino group.

Purpose

The purpose of these studies is to investigate the reducing ability of MgH_2 and its alkoxy derivative toward some representative organic functional groups. Also, it is important to study the stereochemistry of reduction of cyclic and bicyclic ketones of these new classes of magnesium hydride derivatives, HMgOR, $HMgNR_2$ and H_3Mg_2OR, which are considered to be very bulky hydride reagents.

CHAPTER II

EXPERIMENTAL

Note: Preparation of magnesium hydride derivatives used in these studies was carried out by co-worker, Dr. A. B. Goel.[7]

General Considerations

Techniques for handling air-sensitive compounds, apparatus and instrumentations used are the same as previously described in the experimental sections of Part I and Part II.

Analyses

Gas analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Teople pump. Magnesium was determined by EDTA titration. GLPC was performed on F&M Model 720 and 700 gas chromographs.

Materials

These following organic substrate were purchased commercially and used without further purification: 1-iododecane (Eastman), 1-bromodecane (Eastman), 1-chlorodecane (Eastman), 1-iodobenzene (Eastman), benzaldehyde (Eastman), ethyl benzoate (Eastman), nitrobenzene (Fisher), benzoyl chloride (J. T. Baker), 1-octene (Chemical Sample Company), benzyl alcohol (Fisher), and camphor (Eastman). The sources of compounds, 2,2,6,6-tetramethyl-trans-4-hepten-3-one, 4-tert-butylcyclohexanone, 3,3,5-trimethylcyclohexanone and 2-methylcyclohexanone are the same as previously described in the experimental sections of Part I and Part II.

Methanol (Fisher) was distilled after treating with magnesium metal. Isopropanol (Fisher) was distilled over $Al(O\text{-}i\text{-}Pr)_3$ and *tert*-butyl alcohol (Fisher) was fractionally crystallized under nitrogen. 2,6-Dimethylphenol (Aldrich) and 2,6-diisopropylphenol (Ethyl) were distilled before use. Triphenyl carbinol (Eastman) and 2,6-di-*tert*-butyl cresol (Eastman) were used as obtained.

The commercial dialkyl amines, di-*n*-propyl amine (Aldrich), *iso*-propylmethyl amine, di-*iso*-propyl amine (Eastman), di-*s*-butyl amine (Pfaltz & Bauer), piperidine (Fisher) and 2,6-dimethylpiperidine (Aldrich) were dried over molecular sieve 4A and distilled prior to use.

Diethylether and tetrahydrofuran were distilled over $LiAlH_4$ and $HAlH_4$, respectively. Diethylmagnesium was prepared[9] by the reaction of diethylmercury with magnesium metal at 60-80°C and a standard solution in diethylether was made by magnesium analysis.

Preparation of N-(Trimethylsilyl)-*tert*-Butylamine

To a well stirred solution of *tert*-butylamine (50 mmoles) in diethylether in presence of triethylamine, trimethylchlorosilane (50 mmoles) was added dropwise. The reaction was highly exothermic and was cooled down by ice-water bath. An insoluble white solid of $Et_3N.HCl$ formed was removed by filtration and the filtrate was concentrated by distilling the diethylether after which product was distilled at 117-125°C.

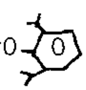
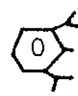
Preparation of MgH_2 Slurry in THF[10]

Lithium aluminum hydride (20.0 mmoles) in diethylether (32 ml) was allowed to react with a diethylether (50 ml) solution of Et_2Mg

(20.0 mmoles) at room temperature under constant stirring for 1 hour. The resulting suspension of MgH_2 was centrifuged, the supernatant liquid was removed via syringe and the precipitate washed with fresh diethylether. This process was repeated and the washed MgH_2 was finally slurried in THF. Anal: calcd. for MgH_2; Mg:H 1.00:2.00. Found; 1.00: 2.02.

Preparation of Alkoxy-Magnesium Hydrides

A known amount of magnesium alkoxide in THF was made by mixing $(CH_3)_2Mg$ in diethylether, with two mole equivalents of the appropriate alcohol followed by heating the mixture at reflux overnight. The diethylether was removed under vacuum and fresh THF added. This magnesium alkoxide was allowed to react with MgH_2 slurried in THF at room temperature with constant stirring for a few hours and analyzed (Table 20).

Another method of preparation was by the direct reaction of the appropriate alcohol with MgH_2 in THF in 1:1 molar ratio, which is exemplified by the following procedure. To a well stirred slurry of MgH_2 (4.0 mmoles) in THF (30 ml) at -78°C, a THF (10 ml) solution of 2,6-diisopropylphenol (4.0 mmoles) was added dropwise. This reaction mixture was allowed to warm to room temperature and stirred for 1 hour to give a clear solution. Anal. calcd. for HMgO  , Mg:H:  OH= 1.00:1.00:1.00. Found: 1.00:0.97:1.04.

Preparation of $ROMg_2H_3$ and $R_2N\ Mg_2H_3$ Compounds

The preparation of H_3Mg_2OR compounds is similar to that described for the preparation of HMgOR, i.e., the reaction of $Mg(OR)_2$ or $Mg(NR_2)_2$ with an active form of MgH_2 in 1:3 molar ratio.

Preparation of Dialkylaminomagnesium Hydrides

The procedure for this preparation were the same as those described for the alkoxymagnesium hydrides except that the appropriate dialkylamine was used instead of the alcohol. The analysis for each compound was satisfactory (Table 29).

General Reactions of Magnesium Hydride Reagents with Model Compounds

The magnesium hydride reagent was added via syringe to a 10 ml. Erlenmeyer flask which had been oven dried, equipped with a magnetic stirrer, cooled under nitrogen and sealed with a rubber septum. The temperature of the flask was then adjusted by either a dry-ice/acetone or ice/water bath. Next, the organic substrate and internal standard were added while stirring vigorously. After the designated reaction time, the reaction solution was quenched slowly with distilled water and dried over $MgSO_4$.

A 10 ft. 5% Carbowax 20 M on Chromosorb W (column A) was used to separate some of the products. The elution time for products (column temperature, 130°C) was in the order of n-tetradecane (internal standard), benzaldehyde, benzonitrile,ethyl benzoate, benzyl alcohol. Products of phenylacetylene and 2,2,6,6-tetramethyl-trans-4-hepten-3-one (see previous parts) were separated by the same column (A). Another column of 6 ft. 10% Apiezon L 60-80S was used to separate 1-iododecane, 1-bromodecane, 1-chlorodecane, iodobenzene, 1-octene and their products. Products were identified by comparing the glc retention time of authentic samples and percentage yields were calculated by suitable hydrocarbon internal standards.

Column A (150°C column temperature) was also used to separate the products of 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, and camphor. A 15 ft. 10% Diglycerol on Chromosorb W column (80°C column temperature) was used to separate the products of 2-methylcyclohexanone. The order of elution for each ketone is the same: the ketone first, the axial or exo alcohol second, and equatorial or endo alcohol last.

CHAPTER III

RESULTS AND DISCUSSION

Functional Group Selectivity

Magnesium hydride and 2,6-diisopropylphenoxymagnesium hydride were allowed to react with some representative organic functional groups in order to investigate their reactivities. The results are summarized in Table 19. Both magnesium hydride and alkoxymagnesium hydrides reduce 1-iododecane to *n*-decane in quantitative yield after 24 hours reaction time at room temperature. 1-Bromodecane, 1-chlorodecane and iodobenzene were found not to be affected by these hydrides. This provides a better selectivity for the reduction of alkyl iodides to hydrocarbons since most known hydride reagents not only reduce alkyl iodides but also alkyl bromides and chlorides under these conditions. For example, $LiAlH_4$ reduces 1-iododecane, 1-bromodecane and 1-chlorodecane under similar conditions (24 h, RT) to give *n*-decane in yields 100, 100 and 68%, respectively.

To determine the reactivity with enones, magnesium hydride and alkoxymagnesium hydride were also allowed to react with 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one (predominantly 1,2 reduction (80-92%)).

To determine the steric requirements of the cyclic ketone reductions, 4-*tert*-butylcyclohexanone was reduced quantitatively to 4-*tert*-butylcyclohexanol and the ratio of cis to trans alcohol was substantially different in both cases, e.g., 24/76 ratio for magnesium hydride and

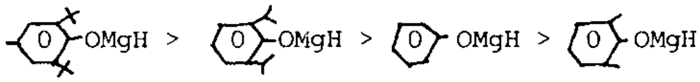
83/17 for 2,6-diisopropylphenoxymagnesium hydride. Formation of cis alcohol in the case of alkoxymagnesium hydride can be explained on steric grounds.

Other carbonyl compounds, benzaldehyde, ethyl benzoate and benzoyl chloride were reduced to produce benzyl alcohol in 80-100% yield. In these reactions, magnesium hydride appears to have a slightly higher reactivity than alkoxymagnesium hydrides. 2,6-Diisopropylphenoxymagnesium hydride as well as magnesium hydride reduce benzaldehyde to benzyl alcohol in 100% yield at -40°C within 1 hour. Under the same condition, ethyl benzoate and benzoyl chloride are reduced to benzyl alcohol in only 8% and 16% yield, respectively. Under more stringent conditions (0° for 1 hour and room temperature for 24 hours) it appears that both compounds are reduced at approximately the same rate although at a rate much slower than that of benzaldehyde. Thus, it would appear that aldehydes can be reduced selectively in the presence of Cl, Br, $\overset{\overset{O}{\|}}{C}$-Cl and $\overset{\overset{O}{\|}}{C}$-OR groups as well as C=C, C≡C and NO_2 (to be discussed later).

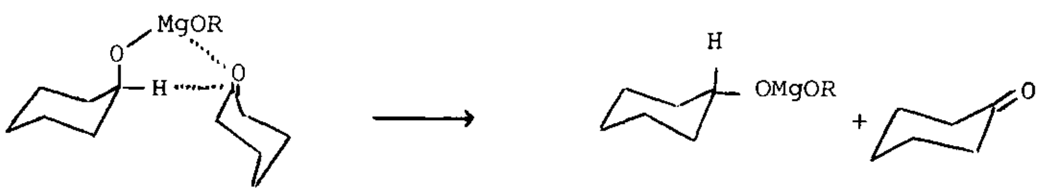
As for the reactions of benzonitrile and nitrobenzene, the expected reduction products were not isolated. Instead unidentified products were formed presumably as a result of free radical polymerization. 1-Octene and phenylacetylene were found to be unreactive toward MgH_2 and 2,6-diisopropylphenoxymagnesium hydride which is actually an advantageous result in terms of functional group selectivity.

Stereoselective Reduction by HMgOR

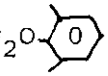
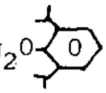
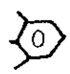
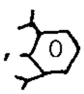
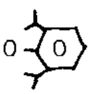
In order to determine the sterochemistry of reduction, the reactions of HMgOR with four representative ketones, 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, 2-methylcyclohexanone and camphor, were examined. MgH_2 and HMgOR (where R = methyl, iso-propyl, tert-butyl, triphenylmethyl, phenyl, 2,6-dimethylphenyl, 2,6-diisopropylphenyl and 2,6-di-t-butyl-4-methylphenyl) were allowed to react with the above four ketones in THF solvent at room temperature. The results are summarized in Tables 21-24. $LiAlH_4$ is considered to be the least sterically hindered hydride. It reduces 4-tert-butylcyclohexanone (I), 3,3,5-trimethylcyclohexanone (II), 2-methyl-cyclohexanone (III) and camphor (IV) by 10, 80, 24 and 9% equatorial (or exo) attack respectively of the reagent on the ketone. On the other hand, MgH_2 reduced ketones I, II, III and IV in 24, 85, 35 and 8% equatorial (or exo) attack respectively. These results can be explained by consideration of the steric requirement of the reagent; the bulkier reagent (highly polymeric MgH_2). MgH_2 should have a higher steric requirement than $LiAlH_4$ in solution. We have also found that the isomer distribution from the reduction of 4-tert-butylcyclohexanone with MgH_2 is dependent upon the ratio of hydride to substrate. For example, the amount of equatorial attack increased from 24% to 61% when the ratio of MgH_2 to ketone was changed from 4:1 to 1:2. Obviously, the alkoxymagnesium hydride which was formed during the reaction process is a bulkier reducing species than MgH_2 itself. The stereoselectivity towards the reaction of cyclic ketones is dependent on the steric requirement of the alkoxy groups and on the aggregation of the hydride reagents. According to the steric bulkiness of the alkoxy group, the degree of stereoselectivity should follow in the order: t-BuOMgH $\approx$ Ph_3COMgH > i-PrOMgH > CH_3OMgH. However, it has been observed that the stereoselectivity is in the order of CH_3OMgH > t-BuOMgH $\geq$ Ph_3COMgH >

i-PrOMgH for 4-*tert*-butylcyclohexanone (76, 69, 71 and 15% equatorial attack, respectively), for 3,3,5-trimethylcyclohexanone (99, 99, 99 and 65% equatorial attack, respectively), for 2-methylcyclohexanone (98, 98, 73 and 68% equatorial attack, respectively) and for camphor (95, 92, 95, and 92% endo attack, respectively). These results are reversed from what is expected unless one takes into account the molecular association of the hydride reagent. Similarly, phenoxymagnesium hydride has a higher degree of molecular association than 2,6,-dimethylphenoxymagnesium hydride, which causes the steric requirement of these hydride reagents to be in the order: 

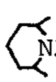
for 4-*tert*-butylcyclohexanone (82, 83, 76 and 67% equatorial attack), for 3,3,5-trimethylcyclohexanone (99.5, 99.5, 99.5 and 94% equatorial attack), for 2-methylcyclohexanone (99, 99, 99 and 80% equatorial attack) and for camphor (98, 98, 99 and 99% endo attack, respectively). When the molar ratio of reagent to ketone is decreased in reactions with MgH_2 and 2,6-di-*tert*-butyl-4-methylphenoxymagnesium hydride there appears to be an equilibrium between the alkoxymagnesium intermediate and the excess ketone. The suggested pathway is similar to that proposed for the Meerwein-Ponndorf-Verley reaction, which causes the isomer distribution to change with time from kinetic to thermodynamic product.



Stereoselective Reduction by H_3Mg_2OR and $H_3Mg_2(NR_2)$

The new magnesium hydride reagents, H_3Mg_2O- , H_3Mg_2O- , H_3Mg_2OMe and H_3Mg_2N(n-Pr)$_2$, were allowed to react with 4-tert-butycyclohexanone (I), 3,3,5-trimethylcyclohexanone (II), 2-methylcyclohexanone (III) and camphor (IV) in order to study the stereoselectivity of these new hydrides. The results are summarized in Tables 25-28. It can be seen that all of the H_3Mg_2OR and $H_3Mg_2NR_2$ compounds react with all four ketones with high stereoselectivity especially in those cases where some group is close enough to the carbonyl group to provide some steric hindrance. For example, H_3Mg_2OR (where R =  ,  and CH_3) reduce the three such ketones in this study in nearly 100% yield and 100% selectivity as a result of equatorial attack. These hydrides reduced 4-tert-butylcyclohexanone with much more equatorial attack (69-91%) than MgH_2 (24%) or $LiAlH_4$(10%) did. Especially, the compound H_3Mg_2O- , is one of the most stereoselective reagents found, which gave 91% equatorial attack towards 4-tert-butylcyclohexanone.

Stereoselective Reduction by $HMgNR_2$

Similarly, it was desireable to determine the steric requirements towards reduction by the newly discovered dialkylaminomagnesium hydrides. To make these determinations, MgH_2, n-Pr_2NMgH, (i-Pr)(Me)NMgH, i-Pr_2NMgH, NMgH, NMgH and $(Me_3Si)(Bu^t)NMgH$ were prepared and allowed to react with four representative ketones. The results are summarized in Tables 30-33.

As before, the stereoselectivity depends on the effective steric bulk of the reducing agent. The effective steric bulk is in turn determined by a size effect of the dialkylamino group and by the extent of aggregation of the hydride reagent. The most selective hydride reagent among those studied is trimethylsilyl-tert-butylaminomagnesium hydride, which reduced ketones I, II, III and IV to give the thermodynamically less stable alcohol in 73, 99, 98 and 95% yields, respectively.

CHAPTER IV

CONCLUSIONS

MgH_2 and 2,6-diisopropylphenoxymagnesium hydride were found to function as active hydride reducing agents. Some representative organic functional groups were reduced to the expected products; the ease of reduction was found to follow the order of benzaldehyde > 4-*tert*-butylcyclohexanone > 2,2,6,6-tetra-methyl-*trans*-4-hepten-3-one> benzoyl chloride > ethyl benzoate > 1-iododecane. In contrast, these hydrides were found to be inert to 1-bromodecane, 1-chlorodecane, iodobenzene, 1-octene and phenylethyne.

Three classes of new magnesium hydrides, HMgOR, H_3Mg_2OR and $HMgNR_2$, were allowed to react with the representative cyclic and bicyclic ketones in order to determine their steric requirements as reducing agents. These hydrides possess a bulky alkoxyl or dialkylamino organic group which enhanced the stereoselectivity of the ketone reductions. The selectivity of these hydride reagents depended on the bulkiness of the substitutent group as well as the aggregation of the hydride reagent.

Table 19. Reactions of Magnesium Hydride (I) and 2,6-Diisopropylphenoxy Magnesium Hydride (II) with Some Representative Functional Groups

Hydride Reagent[a]	Organic Substrate[a]	Reaction Condition	Product(s) and Yield(s)
I	1-Iododecane	-40°C, 1h	*n*-Decane (10)
		0°C, 1h	*n*-Decane (40)
		RT, 24h	*n*-Decane (100)
II	1-Iododecane	-40°C, 1h	*n*-Decane (5)
		0°C, 1h	*n*-Decane (20)
		RT, 24h	*n*-Decane (100)
I	1-Bromodecane	RT, 24h	*n*-Decane (5)
II	1-Bromodecane	RT, 24h	*n*-Decane (5)
I	1-Chlorodecane	RT, 24h	*n*-Decane (0)
II	1-Chlorodecane	RT, 24h	*n*-Decane (0)
I	Iodobenzene	RT, 24h	Benzene (0)
II	Iodobenzene	RT, 24h	Benzene (0)
I	Benzaldehyde	-40°C, 1h	Benzyl Alcohol (100)
II	Benzaldehyde	-40°C, 1h	Benzyl Alcohol (100)
I	Ethyl Benzoate	-40°C, 1h	Benzyl Alcohol (25)

Table 19. (Continued)

Hydride Reagent[a]	Organic Substrate[a]	Reaction Condition	Product(s) and Yield(s)		
I	Ethyl Benzoate	0°C, 1h	Benzyl Alcohol (32)		
		RT, 24h	Benzyl Alcohol (79)		
II	Ethyl Benzoate	-40°C, 1h	Benzyl Alcohol (8)		
		0°C, 1h	Benzyl Alcohol (26)		
		RT, 24h	Benzyl Alcohol (82)		
I	Benzonitrile	-40°C, 1h	Benzonitrile (5)	Benzaldehyde (10)	Benzyl Alcohol (0)
		0°C, 1h	Benzonitrile (35)	Benzaldehyde (15)	Benzyl Alcohol (5)
		RT, 24h	Benzonitrile (0)	Benzaldehyde (3)	Benzyl Alcohol (32)
II	Benzonitrile	-40°C, 1h	Benzonitrile (60)	Benzaldehyde (7)	Benzyl Alcohol (0)
		0°C, 1h	Benzonitrile (40)	Benzaldehyde (32)	Benzyl Alcohol (2)
		RT, 24h	Benzonitrile (0)	Benzaldehyde (8)	Benzyl Alcohol (0)
I	Nitrobenzene	RT, 24h	Nitrobenzene (25)		
II	Nitrobenzene	RT, 24h	Nitrobenzene (20)		
I	Benzoyl Chloride	-40°C, 1h	Benzyl Alcohol (20)		
		0°C, 1h	Benzyl Alcohol (45)		
		RT, 24h	Benzyl Alcohol (85)		
II	Benzoyl Chloride	-40°C, 1h	Benzyl Alcohol (16)		
		0°C, 1h	Benzyl Alcohol (40)		
		RT, 24h	Benzyl Alcohol (85)		

Table 19. (Continued)

Hydride Reagent[a]	Organic Substrate[a]	Reaction Condition	Product(s) and Yield(s)	
I	2,2,6,6-tetra-methyl trans-4-hepten-3-one	RT, 24h	1,4 Product (4)	1,2, Product (92)
II	2,2,6,6-tetra-methyl-trans-4-hepten-3-one	RT, 24h	1,4 Product (7)	1,2 Product (80)
I	1-Octene	RT, 24h	No Reaction	
I	Phenylacetylene	RT, 24h	No reaction	
I	4-tert-butylcyclo-hexanone[b]	RT, 1h	4-tert-butylcyclohexanol (100)[c]	
II	4-tert-butylcyclo-hexanone[b]	RT, 1h	4-tert-butylcyclohexanol (100)[d]	

a. Molar ratio of hydride reagent to substrate is 1:1 for Regent I; 2:1 for Regent II.

b. Molar ratio of hydride reagent to ketone is 4:1.

c. Cis/trans alcohol = 24/76.

d. Cis/trans alcohol = 83/17.

Table 20. Preparation of Alkoxy-Magnesium Hydrides

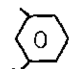
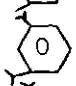
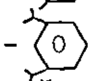
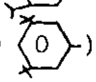
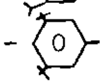
Exp.	Reactants (mmoles) MgH_2	$Mg(OR)_2$	Reaction Time	Solubility in THF	Analysis (Ratio) Mg:H:ROH	Product	
1	5.5	$Mg(OCH_3)_2$ (5.5)	40 h	Insoluble Solid	1.00:0.94:-	$HMgOCH_3$	
2	5.4	$Mg(OPr^i)_2$ (5.35)	24 h	Insoluble Solid	1.00:0.95:-	$HMgOPr^i$	
3	5.1	$Mg(OBu^t)_2$ (5.0)	24 h	Insoluble, Gelatinous Precipitate	1.00:0.95:1.05	$HMgOBu^t$	
4	5.0	Mg(-O )$_2$	48 h	Sparingly Soluble Crystallized from THF	1.00:0.96:1.03	HMgO- 	
5	4.5	Mg(-O )$_2$	2 h	Highly Soluble	1.00:0.98:1.03	HMgO- 	(dimer)
6	4.0	Mg(-O )$_2$	3 h	Highly Soluble	1.00:0.97:1.02	HMgO- 	(dimer)
7	4.2	Mg(-O )$_2$	2 h	Highly Soluble	1.00:0.98:1.03	HMgO- 	(dimer)
8	4.5	$Mg(-OCPh_3)_2$	2 h	Highly Soluble	1.00:0.97:1.04	$HMg(O-CPh_3)$	(dimer)
9	MgH_2		--	Insoluble	1.00:2.02:-	highly assoicated	

Table 21. Reactions of 4-*tert*-Butylcyclohexanone with Alkoxymagnesium Hydrides at Room Temperature in THF Solvent

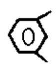
Exp.	Hydrides	Molar Ratio Reagent:Ketone	Reaction Time	Relative Yield Axial-OH	Relative Yield Equatorial-OH	Yield
1	MgH_2	4:1	24h	24	76	100
2	MgH_2	2:1	1h	53	47	100
			24h	53	47	100
3	MgH_2	1:1	1h	56	44	90
			24h	57	43	92
4	MgH_2	1:2	1h	61	39	75
			5h	62	38	77
			24h	45	55	77
5	CH_3OMgH	4:1	24h	76	24	100
6	*i*-PrOMgH	2:1	24h	9	91	45
		4:1	24h	15	85	55
7	*t*-BuOMgH	4:1	24h	69	31	90
8	Ph_3COMgH	4:1	24h	71	29	100
9	 -OMgH	4:1	24h	76	24	100
10	 -OMgH	4:1	24h	68	32	100
		1:1	24h	60	40	92
		0.5:1	24h	12.5	87.5	55

Table 21. (Continued)

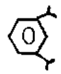
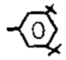
Exp.	Hydrides	Molar Ratio Reagent:Ketone	Reaction Time	Relative Yield Axial-OH	Equatorial-OH	Yield
11	 -OMgH	4:1	24h	83	17	100
12	 -OMgH	4:1	24h	82	18	100
		1:1	24h	80	20	100
		0.5:1	24h	56	44	55

Table 22. Reactions of 3,3,5-Trimethylcyclohexanone with Alkoxymagnesium Hydrides at Room Temperature in THF Solvent and 4:1 Molar Ratio of Reagent: Ketone

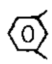
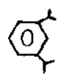
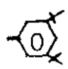
		Relative Yield		
Exp.	Hydride	Axial-OH	Equatorial-OH	Yield
13	MgH_2	85	15	92
14	CH_3OMgH	99	1	70
15	i-PrOMgH	65	35	40
16	t-BuOMgH	99	1	65
17	Ph_3COMgH	99	1	98
18	 -OMgH	<99.5	<0.5	100
19	 -OMgH	94	6	52
20	 -OMgH	99.5	0.5	100
21	 -OMgH	<99.5	<0.5	100

Table 23. Reactions of 2-Methylcyclohexanone with Alkoxymagnesium Hydrides at Room Temperature in THF Solvent and 4:1 Molar Ratio of Reagent:Ketone

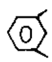
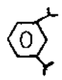
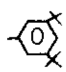
Exp.	Hydride	Relative Yield Axial-OH	Relative Yield Equatorial-OH	Yield
22	MgH_2	35	65	100
23	CH_3OMgH	98	2	97
24	i-PrOMgH	68	32	30
25	t-BuOMgH	98	2	96
26	Ph_3COMgH	73	27	100
27	 -OMgH	99	1	100
28	 -OMgH	80	20	100
29	 -OMgH	99	1	100
30	 -OMgH	99	1	100

Table 24. Reactions of Camphor with Alkoxymagnesium Hydrides at Room Temperature in THF Solvent and 4:1 Molar Ratio of Reagent:Ketone

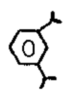
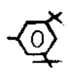
Exp.	Hydride	Relative Yield Endo-OH	Relative Yield Exo-OH	Yield
31	MgH_2	8	92	100
32	CH_3OMgH	5	95	40
33	*i*-PrOMgH	8	92	15
34	*t*-BuOMgH	8	92	20
35	Ph_3COMgH	5	95	100
36	 -OMgH	1	99	100
37	 -OMgH	1	99	100
38	 -OMgH	2	98	100
39	 -OMgH	2	98	100

Table 25. Reactions of 4-*tert*-Butylcyclohexanone with H_3Mg_2OR and $H_3Mg_2NR_2$ in THF, 1:1 Molar Ratio of Reagent:Ketone

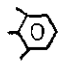
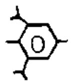
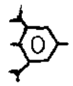
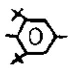
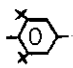
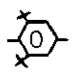
Exp.	Hydride	Reaction Condition	Relative Yield Axial-OH	Relative Yield Equatorial-OH	Yield
40	H_3Mg_2O 	RT 24h	72	28	100
41	H_3Mg_2O 	RT 24h	78	22	100
42	H_3Mg_2O 	0°C 24h	91	9	85
43	H_3Mg_2O 	RT 24h	69	31	100
44	H_3Mg_2O 	0°C 24h	74	26	100
45	H_3Mg_2O 	RT 24h	70	30	98-99
46	H_3Mg_2OMe	RT 24h	71	29	95
47	$H_3Mg_2NPr^n_2$	RT 5h	75	25	70
		RT 24h	75	25	72

Table 26. Reactions of 3,3,5-Trimethylcyclohexanone with H_3Mg_2OR and $H_3Mg_2NR_2$ in THF, 1:1 Molar Ratio of Reagent:Ketone

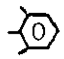
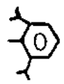
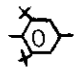
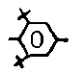
Exp.	Hydride	Reaction Condition	Relative Yield Axial-OH	Relative Yield Equatorial-OH	Yield
48	H_3Mg_2O 	RT 24h	99.5	0.5	100
49	H_3Mg_2O 	RT 24h	100	0	100
50	H_3Mg_2O 	RT 24h	100	0	100
51	H_3Mg_2O 	0°C 24h	100	0	100
52	H_3Mg_2OMe	RT 24h	99.5	0.5	99
53	$H_3Mg_2NPr^n_2$	RT 24h	99.5	0.5	85

Table 27. Reaction of 2-Methycyclohexanone with H_3Mg_2OR and $H_3Mg_2NR_2$ in THF, 1:1 Molar Ratio of Reagent:Ketone

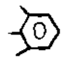
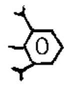
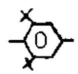
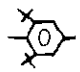
Exp.	Hydride	Reaction Condition	Relative Yield Axial-OH	Equatorial-OH	Yield
54	H_3Mg_2O 	RT 24h	99	1	100
55	H_3Mg_2O 	RT 24h	99	1	100
56	H_3Mg_2O 	RT 24h	100	0	100
57	H_3Mg_2O 	0°C 24h	100	0	100
58	H_3Mg_2OMe	RT 24h	99.5	0.5	96
59	$H_3Mg_2NPr^n_2$	RT 24h	99	1	80

Table 28. Reactions of Camphor with H_3Mg_2OR and H_3Mg_2NR in THF, 1:1 Molar Ratio of Reagent:Ketone

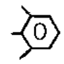
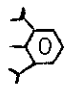
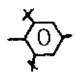
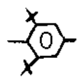
Exp.	Hydride	Reaction Condition	Relative Yield exo-OH	endo-OH	Yield
60	H_3Mg_2O 	RT 24h	99	1	100
61	H_3Mg_2O 	RT 24h	99.5	0.5	100
62	H_3Mg_2O 	RT 24h	99.5	0.5	100
63	H_3Mg_2O 	0°C 24h	99.5	0.5	100
64	H_3Mg_2OMe	RT 24h	99.5	0.5	100
65	$H_3Mg_2NPr^n_2$	RT 24h	98	2	65

Table 29. Preparation of Dialkylaminomagnesium Hydrides in THF

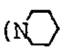
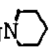
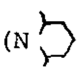
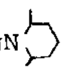
Exp.	Reactants (mmoles) MgH_2	$Mg(NR_2)_2$	Reaction Time (h)	Analysis (Ratio) Mg:H	Probable Compound	Solubility in THF
1	6.0	$Mg(NPr^n_2)_2$ (6.00)	1h	1.00:0.97	$HMgNPr^n_2$	Highly soluble
2	5.85	$Mg(NPr^i_2)_2$ (5.90)	1h	1.00:0.96	$HMgNPr^i_2$	Highly soluble
3	5.90	$Mg(N\langle^{Pr^i}_{Me})_2$ (5.90)	3h	1.00:0.96	$HMgN\langle^{Me}_{Pr^i}$	Less soluble, cyrstallized out from THF
4	6.00	$Mg(NBu^s_2)_2$ (5.95)	2h	1.00:0.97	$HMgNBu^s_2$	Fairly soluble, could be crystallized from THF
5	6.00	Mg()$_2$ (5.96)	3h	1.00:0.95	HMg	Less soluble, crystallized from THF
6	5.50	Mg()$_2$ (5.50)	2h	1.00:0.96	HMg	Less soluble, crystallized from THF

Table 29. (Continued)

Exp.	Reactants (mmoles) MgH_2	$Mg(NR_2)_2$	Reaction Time (h)	Analysis (Ratio) Mg:H	Probable Compound	Solubility in THF
7	6.05	$Mg(N(Bu^t)(SiMe_3))_2$	1.5h	1.00:0.97	$HMgN(Bu^t)(SiMe_3)$	Highly soluble in THF

All the reactions have been carried out at room temperature in THF (50-60 ml).

Table 30. Reactions of 4-*tert*-Butylcyclohexanone with Dialkylaminomagnesium Hydrides in THF at Room Temperature, 24h, 4:1 Molar Ratio at Reagent:Ketone

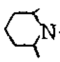
Exp.	Hydride	Relative Axial-OH	Yield Equatorial-OH	Yield
66	MgH_2	24	76	100
67	*n*-Pr_2NMgH	60	40	65
68	(*i*-Pr)(Me)NMgH	38	62	50
69	*i*-Pr_2NMgH	57	43	60
70	*s*-Bu_2NMgH	59	41	55
71	NMgH	63	37	39
72	N-MgH	45	55	70
73	Me_3Si(Bu^t)NMgH	73	27	75

Table 31. Reactions of 3,3,5-Trimethylcyclohexanone with Dialkylaminomagnesium Hydrides in THF at Room Temperature, 24h, 4:1 Molar Ratio of Reagent: Ketone

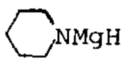
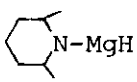
Exp.	Hydride	Relative Axial-OH	Yield Equatorial-OH	Yield
74	MgH_2	85	15	92
75	*n*-Pr_2NMgH	98	2	46
76	(*i*-Pr)(Me)NMgH	95	5	29
77	*i*-Pr_2NMgH	95	1	75
78	*s*-Bu_2NMgH	99.5	0.5	70
79		98	2	35
80		94	6	52
81	$(Me_3Si)(Bu^t)NMgH$	99	1	82

Table 32. Reactions of 2-Methylcyclohexanone with Dialkylaminomagnesium Hydrides in THF at Room Temperature, 24h, 4:1 Molar Ratio of Reagent:Ketone

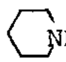
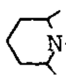
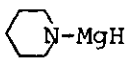
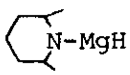
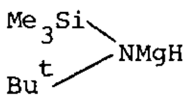
Exp.	Hydride	Relative Yield Axial-OH	Equatorial-OH	Yield
82	MgH_2	35	65	100
83	n-Pr_2NMgH	90	10	28
84	(i-Pr)(Me)NMgH	80	20	40
85	i-Pr_2NMgH	98.5	1.5	85
86	s-Bu_2NMgH	98	2	62
87	NMgH	92	8	40
88	N-MgH	82	18	58
89	(Me_3Si)(Bu^t)NMgH	98	2	95

Table 33. Reactions of Camphor with Dialkylaminomagnesium Hydrides in THF at Room Temperature, 24h, 4:1 Molar Ratio of Reagent:Ketone

Exp.	Hydride	Relative Endo-OH	Yield Exo-OH	Yield
90	MgH_2	8	92	100
91	n-Pr_2NMgH	13	87	92
92	(i-Pr)(Me)MgH	10	90	15
93	i-Pr_2NMgH	7	93	45
94	s-Bu_2NMgH	6	94	55
95		12	88	10
96		7	93	42
97		5	95	100

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PART V

REACTIONS OF LITHIUM ALUMINUM HYDRIDE-TRANSITION METAL HALIDES WITH ALKENES, ALKYNES AND ALKYL HALIDES

CHAPTER I

INTRODUCTION

Background

Application of transition metal hydrides in organic synthesis has been an area of interest in recent years. Although the ability of transition metal hydrides to add to olefins to form carbon to metal bonds has been known for some years,[1] the synthetic utility of this reaction is still under development.

Recently, hydrozirconation of alkenes and alkynes has been shown to yield a versatile intermediate for useful synthetic transformations.[2] Besides the zirconium hydride (Cp_2ZrHCl), $LiAlH_4$-catalytic $ZrCl_4$[3] has been reported to reduce terminal alkenes and $LiAlH_4$-stoichiometric $TiCl_4$[4] was found to be useful for the reduction of alkynes and mono-substituted alkenes. The applicability of these reagents has been limited by low reactivity with higher substituted or strained olefins. Meanwhile, it is also interesting to investigate other transition metal halides which could be more reactive or more useful than those of zirconium and titanium.

Another application of transition metal hydrides is to reduce organic halides to corresponding hydrocarbons. Recently, $LiAlH(OCH_3)_3$-CuI[5] and LiCuHR[6] compounds (where R = alkyl and alkynyl) were evaluated as reagents for removal of halo and mesyloxyl groups. The reagents, $TiCl_3$-Mg[7] and $(\pi\text{-}Cp)_2TiCl_2$-Mg[8] were used for the same purpose at almost the same time by different research groups. More recently in this research group, a series of complex copper hydrides (Li_nCuH_{n+1}) were prepared and have shown the ability of removing the halo and tosylate group.[9] However, the above reagents were either difficult to prepare or had low reactivity toward halide reduction. It would be important to find other reagents which can effect halide reductions efficiently and economically.

Purpose

To study the effect of first row transition metal halides on $LiAlH_4$ toward the reduction of alkenes, alkynes and alkyl halides is the purpose of this study. Also, an understanding of the mechanism and the intermediates of hydrometalation reactions is desired.

CHAPTER II

EXPERIMENTAL

General Considerations

Techniques for handling air-sensitive compounds, apparatus and instruments used are the same as previously described in the experimental sections of Part I and Part II.

Materials

Tetrahydrofuran (Fisher Certified Reagent Grade) was distilled under nitrogen over $NaAlH_4$. Lithium aluminum hydride solutions were prepared by refluxing $LiAlH_4$ (Alfa Inorganics) in THF overnight followed by filtration through a fritted glass funnel in a dry box. The concentration was determined by Al analysis. Transition metal halides, $TiCl_3$, $CrCl_3$, $MnCl_2$, $ZnBr_2$ (Fisher), VCl_3, $FeCl_3$, $FeCl_2$, $CoCl_2$ and $NiCl_2$ (Alfa) were opened only in a dry box and used without further purification. All organic substrates were purchased commercially and used without further purification. 1-Octene, 1-methyl-1-cyclohexene, styrene, _cis_-2-hexene, _trans_-2-hexene, 2-ethyl-1-hexene, cyclohexene, phenylethyne, diphenylethyne, 1-octyne and 2-hexyne were obtained from Chemical Sample Company or Aldrich Chemical Company. Halide substrates were purchased from the following companies: iodo-, bromo-, chloro- and fluorodecane, 1-bromoadamantane, iodo-, bromo-, and chlorobenzene (Eastman), chloro- and bromocyclohexene (Aldrich), 3-bromooctane (Columbia Organic Chemical Company). _n_-Octyl tosylate was prepared by the same procedures as described in Part III.

General Reactions of Alkene, Alkyne and Halide

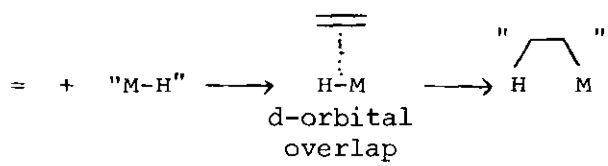
A 10 ml Erlenmeyer flask with a teflon coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen flush. Transition metal halide (ca. 3 mmole scale for stoichiometric reaction and ca. 1 mmole for catalytic reaction) was transferred to the flask in the dry box. The flask was sealed with a rubber septum, removed from the box and connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil-filled bubbler. One or two ml THF was introduced into the reaction vessel and then the olefin or alkyne added. The resulting solution was cooled by means of a dry ice-acetone bath before adding the desired amount of $LiAlH_4$. After 10 minutes, the reaction was warmed to the desired temperature (-40°C, -20°C or RT). The reaction was quenched by water and worked up by the regular method; extracted with THF and dired over $MgSO_4$. Most products were separated by glc using a 6 ft. 10% Apiezon L 60-80 S column: 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 for 1-hexene, cis-2-hexene, trans-2-hexene and 2-hexyne (50°C); a 10 ft. 5% Carbowax 20 M column for phenylethyne (90°C) and diphenylethyne (200°C). The yield was calculated by using a suitable hydrocarbon internal standard for each case and the products were identified by comparing the retention times of authentic samples. Yields of cis-stilbene (δ6.60, vinyl H), trans-stilbene (δ7.10, vinyl H) and 1,2-diphenylethane (δ2.92 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 glc. The yield of adamantane (δ1.88 and 1.77) was determined by NMR and glc (Apiezon column). The compound, adamantane, was isolated and characterized by melting point, mp 206-210°C (lit. 205-210°C) and mass spectrum, M^{+} 136.5 (expected 136.2). The determination of % yield for halide reactions has been already described in Part III.

CHAPTER III

RESULTS AND DISCUSSION

Reactions of 1-Octene

The monosubstituted olefin, 1-octene, was chosen for this initial study. The results are shown in Table 34. High yields of octane are obtained using $TiCl_3$, $CrCl_3$, $FeCl_2$, $FeCl_3$, $CoCl_2$ or $NiCl_2$ and lithium aluminum hydride. $LiAlH_4$-VCl_3 and $LiAlH_4$-$MnCl_2$ both had lower activities and $LiAlH_4$-CuI and $LiAlH_4$-$ZnBr_2$ had no activity toward olfin reduction. The reactive species is presumed to be a transition metal hydride and the reducing ability of the reagent is believed to be due to d-orbital overlap between the metal atom and the unsaturated carbon-carbon bond. Under this assumption, $Cu^{I}(d^{10})$ and $Zn^{II}(d^{10})$



have no empty d-orbitals to overlap with the olefin and $Mn^{II}(d^5)$ with the d-orbitals half filled should be predicted to have a lower activating ability. This explanation is consistant with the results obtained.

In order to investigate the catalytic properties of the first row transition metal halides, a 1.0:0.10:1.0 ratio of $LiAlH_4$:metal halide:1-octene was used in reactions 11-18 in Table 35. The results show clearly that 1-octene can be reduced to *n*-octane by the combination of $LiAlH_4$ with a catalytic amount of $CoCl_2$, $NiCl_2$ or $TiCl_3$. The same reaction was weakly catalyzed by VCl_3 or $CrCl_3$, but no catalytic behavior was observed with $MnCl_2$, $FeCl_2$ or $FeCl_3$.

In Table 36, the results of reactions with a 1.0:1.0 ratio of hydride:1-octene are shown. The recovery of 1-octene was considered to be equivalent to the amount of transition metal hydride decomposed during the reaction. In the cases of $FeCl_2$ and $TiCl_3$, the hydrometalation reactions were complete before the hydride decomposed. On the other hand, these results have demonstrated that all four hydrogen atoms from lithium aluminum hydride are available for such reactions.

Reactions of 1-Methyl-1-Cyclohexene

The trisubstituted olefin, 1-methyl-1-cyclohexene was allowed to react with $LiAlH_4$-transition metal halide. This olefin, which is somewhat sterically hindered, was not affected by hydrozirconation.[2] Table 37 shows that this olefin can be transformed to the saturated hydrocarbon by $LiAlH_4$-$FeCl_2$ in 27-30% yield and also can be reduced by either $LiAlH_4$-$CoCl_2$ (1:1) or $LiAlH_4$-$NiCl_2$ (1:1) in high yields (91-96%). The success of reducing 1-methylcyclohexene has revealed that cobalt (II) and nickel (II) salts possess higher ability than iron (II) or other first row transition metal halides toward hydrometalation. It is also important to note this same reaction can not be carried out catalytically using $CoCl_2$, $NiCl_2$ nor $TiCl_3$.

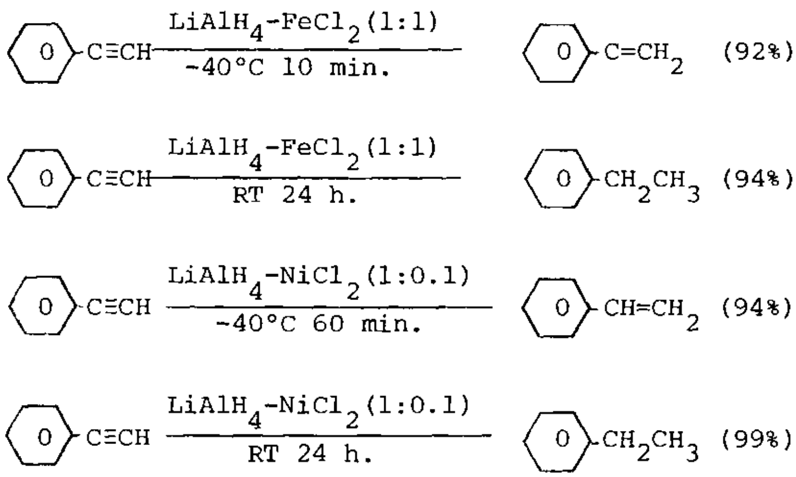
Reactions of Styrene, 1-Hexene, 2-Ethyl-1-Hexene, *Cis*-2-Hexene, *Trans*-2-Hexene and Cyclohexene

Monosubstituted olefins, styrene and 1-hexene, were reduced to ethylbenzene and n-hexane in high yields by $LiAlH_4$-equivalent molar ratio of $FeCl_2$ or catalytic $CoCl_2$, $NiCl_2$ or $TiCl_3$ at room temperature 24 h (Table 38). Disubstituted olefins, such as 2-ethyl-1-hexene, cis- and trans-2-hexene and cyclohexene, were also reduced by $LiAlH_4$-$FeCl_2$ (1:1 ratio). The catalytic amounts of $CoCl_2$, $NiCl_2$ or $TiCl_3$ affected the reduction of these disubstituted olefins at a much slower rate than that of monosubstituted olefins. However, when the stoichimetric amounts of $CoCl_2$, $NiCl_2$ or $TiCl_3$ were used, the rate of the reaction accelerated and high yields of the products were obtained.

Reactions of Phenylethyne

The terminal alkyne, phenylethyne, was allowed to react with $LiAlH_4$-transition metal halides. When the transition metal was VCl_3, $CrCl_3$ or $MnCl_2$, phenylethyne was reduced to yield styrene and ethylbenzene without selectivity. Both products appeared from the beginning of the reaction (expts. 70, 72 and 74), showing the competitive reaction between the alkyne and the alkene reductions. In addition, the ratio of $LiAlH_4$:metal halide:substrate seems to be important in suppressing side reactions. For example, the ratio of 1:1:2 had improved mass balance compared to the ratio of 1:1:3.5. The reaction of $LiAlH_4$-$FeCl_2$ with phenylethyne was studied carefully, (expts. 75, 76, 77 and 78). The mass balance was increased by decreasing substrate to reagent ratio as observed in other metal halide cases. When the ratio is 1:1:2, $LiAlH_4$:metal halide:substrate, the desired product, styrene or ethylbenzene, can be obtained by early quenching before 10 minute reaction time at -40°C (92% styrene, 0% ethylbenzene) or late quenching after 24 hours at room temperature (85% ethylbenzene, 1% styrene). However, 94% ethylbenzene can also be reached at the ratio of 1:1: at 24 h RT reaction conditions.

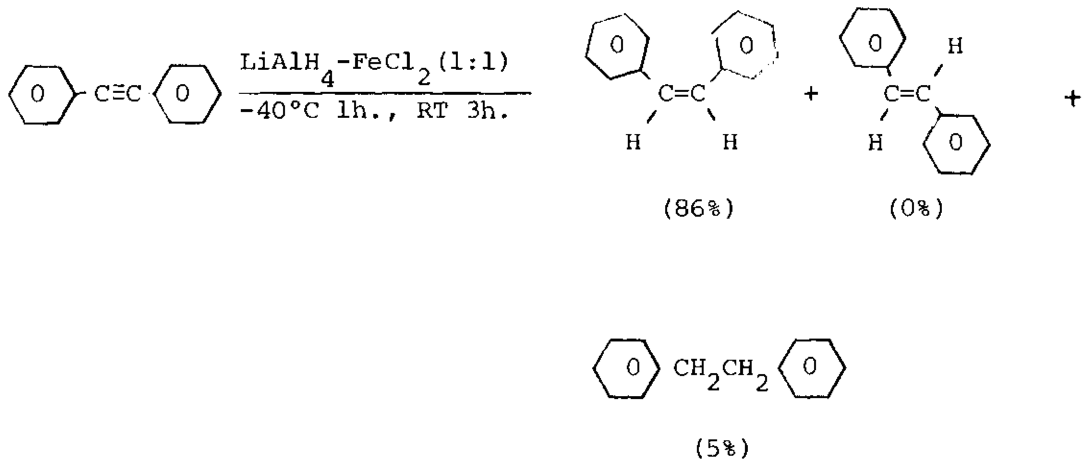
Ferric chloride behaved in a similar fashion as $FeCl_2$ but with a lower mass balance (expts. 79-80). It is also important to note that the catalytic amount of $NiCl_2$ produced the same results as a stoichiometric amount of $FeCl_2$, selectively producing 94% yield of styrene under the reaction conditions of exp. 85 or 99% yield of ethylbenzene in exp. 86.



The reaction of catalytic $TiCl_3$ was comparably slower and reactions of both $TiCl_3$ and $CoCl_2$ had inferior selectivities than that of $NiCl_2$.

Reactions of Diphenylethyne

Three products were observed in reactions with diphenylethyne; *i.e.*, *cis*-stilbene, *trans*-stilbene and 1,2-diphenylethane. Reactions of $LiAlH_4$-VCl_3, $CrCl_3$ or $MnCl_2$ with diphenylethyne were similar to the reaction of phenylethyne, no selectivity toward product distribution was seen. However, *cis*-stilbene (100% stereoselectivity and 86% yield) was obtained by the reaction of $LiAlH_4$-$FeCl_2$.



Both $CoCl_2$ and $NiCl_2$ were also studied by varying the ratio of reagent:substrate, the reaction temperature and the catalytic abilities. In general, cis-reduction was observed when lower reaction temperatures (-20°C or -40°C) and shorter reaction times were employed. Slight isomerization to the more stable trans-stilbene did occur with longer reaction times at room temperature. However, the catalytic reaction with $NiCl_2$ produced 75% cis-stilbene, 15% 1,2-diphenylethane with 100% stereoselectivity for the cis reaction after 24 h. reaction time at room temperature. The reaction of $TiCl_3$ at -40°C was much slower than either $NiCl_2$ or $CoCl_2$.

Reactions of 1-Octyne and 2-Hexyne

For the reduction of aliphatic alkynes, $LiAlH_4$-$FeCl_2$(1:1) reacted with 1-octyne and 2-hexyne to produce 1-octene, octane and cis-, trans-2-hexene and hexane, respectively (Table 41). This, then, shows little selectivity. Reaction involving $LiAlH_4$-$CoCl_2$(1:0.1) had similar results. However, excellent selectivity in reduction obtained by the reagent $LiAlH_4$-$NiCl_2$(1:0.1) which reduced 1-octyne to 1-octene in 99% yield with only 0-1% octane formed and reduced 2-hexyne to cis-2-hexene in 91% yield with 0% trans-2-hexene and 4% hexane.

Reactions of Organohalides

Lithium aluminum hydride is not an effective reagent for the removal of halo or tosylate groups from organic molecules other than primary halides and tosylates. For example, $LiAlH_4$ reduces 1-iododecane, 1-bromodecane and n-octyl tosylate to the corresponding hydrocarbon in 92-98% yields, but reduces 1-chlorodecane in only 68% yield in a much longer time and exhibits no effect at all in the reduction of bromocyclohexane and bromobenzene under the same reaction conditions (room temperature, 24 h, stoichiometric 1:1 molar ratio of $LiAlH_4$: halide substrate).[9] The admixture of $LiAlH_4$-transition metal chloride (VCl_3, $CrCl_3$, $MnCl_2$, $FeCl_2$, $FeCl_3$, $CoCl_2$, $NiCl_2$ and $TiCl_3$) in stoichiometric or catalytic amount was allowed to react with the alkyl or aryl halide in order to compare the reactivity of these mixed reagents with $LiAlH_4$ itself. The results are shown in Table 42.

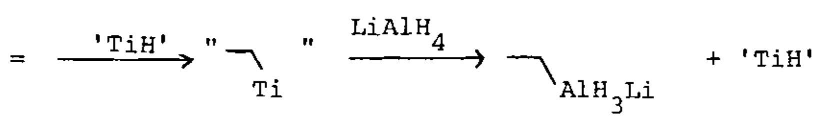
In the reactions of 1-chlorodecane and 1-bromodecane, $FeCl_2$, $CoCl_2$, $NiCl_2$ and $TiCl_3$ (stoichiometric or catalytic) show superior reducing ability compared to the other catalysts evaluated, i.e., VCl_3, $CrCl_3$, $MnCl_3$ and $FeCl_3$. The admixture of $LiAlH_4$-stoichiometric VCl_3, $CrCl_3$ and $MnCl_2$ reduced 1-chloro and 1-bromodecane to n-decane in only low yields compared to the reactions involving $FeCl_2$, $CoCl_2$, $NiCl_2$ and $TiCl_3$ under the same reaction conditions. Furthermore, $LiAlH_4$ with 10 mole % $FeCl_2$, $CoCl_2$, $NiCl_2$ and $TiCl_3$ reduced 1-chlorodecane in 85, 100, 100 and 100% yields, respectively. These results reveal the relative catalytic ability of transition metal chlorides, i.e. $CoCl_2$, $NiCl_2$ and $TiCl_3$ are more effective catalysts than $FeCl_2$.

Since $FeCl_2$, $CoCl_2$, $NiCl_2$ and $TiCl_3$ admixed with $LiAlH_4$ were found to be the most effective catalysts for reduction of 1-chloro- and 1-bromodecane, only these catalysts were used in further studies of other halides. Decyliodide was reduced to n-decane in nearly quantitative yield by the above transition metal halides, however, fluorodecane was reduced in only 7-16% yield. n-Octyl tosylate was reduced to n-octane in 98-100% yield by $LiAlH_4$ and a catalytic amount (10 mole %) of $NiCl_2$ and $CoCl_2$ but in significantly lower yields by $FeCl_2$ and $TiCl_3$. The secondary halide, 3-bromodecane, was also reduced in high yield (88-98%) when the transition metal halides were used in stoichiometric amount. Bromocyclohexane and chlorocyclohexane, which are inert to $LiAlH_4$, can be reduced by $LiAlH_4$ with stoichiometric amounts of $FeCl_2$, $CoCl_2$, $NiCl_2$ or a catalytic amount (10 mole %) of $TiCl_3$ to produce cyclohexane in excellent yield (92-100%). However, a catalytic amount (10 mole %) of $CoCl_2$ or $NiCl_2$ was not effective in the reduction of bromocyclohexane. Also, 1-bromoadamantane was reduced to adamantane in quantitative yield by all four catalysts.

Phenyl halides (X = I, Br and Cl) were also allowed to react with these new reagents. The substrates were reduced in the order l>Br>Cl and the superior reagent for the reduction of aromatic halides was found to be $LiAlH_4$:$NiCl_2$ (1:1) which reduced iodo-, bromo- and chlorobenzene to benzene in 100% yield.

Deuterium Incorporation

In order to determine the nature of the reaction intermediate of alkene reduction by $LiAlH_4$ with 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 deuterated and non-deuterated product in the mass spectrum. The results are summarized in Table 43. In the reaction involving stoichiometric amounts of $FeCl_2$ or catalytic amounts of $CoCl_2$ and $NiCl_2$, the content of d-octane was only 12-26% based on the total octane product. The only experiment yielding high amounts of deuterium incorporation was the reaction with $TiCl_3$ (94% d-incorporation). These results imply that the hydrometalation intermediate is not stable under the conditions studied except in the case of $TiCl_3$. In other words, the transmetalation reaction from alkyl transition metal to alkyl aluminum intermediate proceeded only in the case of $TiCl_3$.



Several experiments were attempted to stabilize the carbon-transition metal bond by varying the ligands attached to the transition metal. It is expected that the ligands are capable of stabilizing the transition metal compounds by dispersing the d-orbitals of the transition metal through the attached ligands. Two equivalents of triphenylphosphine was added to $NiCl_2$, which resulted in higher deuterium incorporation (37-42%) and lower rates of reduction. Other nickel halides, cyclopentadienyl nickel chloride (CpNiCl) and bis-cyclooctadienyl nickel ($(COD)_2Ni$) in the presence of two equivalents of triphenylphosphine, gave 27 and 47% deuterium incorporation, respectively.

Although the maximum deuterium incorporation has only reached 47%, the significant improvement compared to $NiCl_2$ shows the stability of the hydrometal intermediate can be increased using ligands. However, more satisfactory results are still under development.

CHAPTER IV

CONCLUSIONS

Reactions of $LiAlH_4$-first row transition metal halides ($TiCl_3$, VCl_3, $CrCl_3$, $MnCl_2$, $FeCl_2$, $FeCl_3$, $CoCl_2$, $NiCl_2$, CuI and $ZnBr_2$) with the monosubstituted alkenes (1-octene, 1-hexene and styrene), disubstituted alkenes (2-ethyl-1-hexene, cis-2-hexene, trans-2-hexene and cyclohexene), and trisubstituted alkenes (1-methyl-1-cyclohexene) as well as terminal alkynes (phenylethyne and 1-octyne) and internal alkynes (diphenylethyne and 2-hexyne) have been studied. The ability of alkenes to be reduced by $LiAlH_4$-transition metal halide was found to be in the order: Co(II) > Ni(II) > Fe(II) ≈ Fe(III) > Ti(III) > Cr(III) > V(III) > Mn(II) > Cu(I) ≈ Zn(II). Admixtures of $LiAlH_4$-CuI and $LiAlH_4$-$ZnBr_2$ were not effective in alkene reduction. $CoCl_2$, $NiCl_2$ and $TiCl_3$ can catalyze the $LiAlH_4$ reduction of monosubstituted alkenes. VCl_3 and $CrCl_3$ have partial catalytic ability and no catalytic activity was observed for $MnCl_2$, $FeCl_2$ and $FeCl_3$. Catalysis is slower for disubstituted and trisubstitued alkenes compared to the corresponding monosubstituted compounds.

Reduction of alkynes can be carried out quantitatively to give alkenes and alkanes depending on the transition metal halide used as a catalyst, the ratio of reagent to substrate and the reaction conditions. The best reagent is $LiAlH_4$-$NiCl_2$ from the point of view of product selectivity. A cis reduction mechanism was indicated from cis-olefin product isolation..

Alkyl halides (1°, 2° and 3°) and aryl halides can be reduced to the corresponding hydrocarbons efficiently and quantitatively by reaction with $LiAlH_4$ containing a catalytic or stoichiometric amount of a first row transition metal chloride at room temperature in tetrahydrofuran.

Table 34. Reactions of 1-Octene with $LiAlH_4$-Transition Metal Halides in 1.0:1.0:0.5 Molar Ratio of $LiAlH_4$:Metal Halide:1-Octene at RT

Exp.	Metal Halides	Reaction Time[a]	1-Octene Recovery (%)	Octane (%)
(1)	$TiCl_3$	1 h	0	98
(2)	VCl_3	1 h	100	0
		8 h	0	93
(3)	$CrCl_3$	1 h	0	100
(4)	$MnCl_2$	1 h	71	25
		8 h	53	40
(5)	$FeCl_2$	1 h	0	98
(6)	$FeCl_3$	1 h	0	98
(7)	$CoCl_2$	1 h	0	100
(8)	$NiCl_2$	1 h	0	100
(9)	CuI	8 h	95	~5
(10)	$ZnBr_2$	8 h	100	0

a. Reaction time was counted after removing the cooling system.

Table 35. Reactions of 1-Octene with $LiAlH_4$-Transition Metal Halides in 1.0:0.10:1.0 Molar Ratio of $LiAlH_4$:Metal Halide:1-Octene at RT

Exp.	Metal Halides	Reaction Time	1-Octene Recovery	Octane (%)
(11)	VCl_3	18 h	64	42
(12)	$CrCl_3$	18 h	80	19
(13)	$MnCl_2$	18 h	100	0
(14)	$FeCl_2$	18 h	95	5
(15)	$FeCl_3$	18 h	95	5
(16)	$CoCl_2$	18 h	0	98
(17)	$NiCl_2$	18 h	~5	94
(18)	$TiCl_3$	18 h	~0	95

Table 36. Reactions of 1-Octene with $LiAlH_4$-Transition Metal Halide in 1.0:1.0:4.0 Molar Ratio of $LiAlH_4$:Metal Halide:1-Octene at RT

Exp.	Metal Halide	Reaction Time	1-Octene Recovery (%)	Octane (%)
(19)	VCl_3	18 h	8	90
(20)	$CrCl_3$	18 h	6	91
(21)	$FeCl_2$	18 h	~0	96
(22)	$FeCl_3$	18 h	18	80
(23)	$CoCl_2$	18 h	17	80
(24)	$NiCl_2$	18 h	17	82
(25)	$TiCl_3$	18 h	0	96

Table 37. Reactions of 1-Methyl-1-Cyclohexene with $LiAlH_4$-Transition Metal Halides at RT

Exp.	Metal Halide	Molar Ratio $LiAlH_4$:Metal Halide:Substrate	1-Methyl-Cyclohexene Recovery (%)	Methylcyclohexane (%)
(26)	VCl_3	1:1:2	100	0
(27)	$CrCl_3$	1:1:2	100	0
(28)	$MnCl_2$	1:1:2	100	0
(29)	$FeCl_2$	1:1:2	67	27
(30)	$FeCl_2$	1:1:0.5	70	30
(31)	$CoCl_2$	1:0.1:2	98	2
(32)	$CoCl_2$	1:1:0.5	0	96
(33)	$CoCl_2$	1:1:1	0	91
(34)	$NiCl_2$	1:0.1:2	100	0
(35)	$NiCl_2$	1:1:1	0	94
(36)	$TiCl_3$	1:0.1:2	100	0
(37)	$TiCl_3$	1:1:1	94	2

Table 38. Reactions of Other Alkenes with $LiAlH_4$-Transition Metal Halides at RT

Exp.	Metal Halide	Alkene Substrate	Reaction Condition	Substrate Recovery (%)	Alkane Yield (%)
(38)	$FeCl_2^a$	Styrene	24 h	0	Ethylbenzene (95)
(39)	$CoCl_2^b$	Styrene	24 h	5	Ethylbenzene (92)
(40)	$NiCl_2^b$	Styrene	24 h	0	Ethylbenzene (92)
(41)	$TiCl_3^b$	Styrene	24 h	0	Ethylbenzene (94)
(42)	$FeCl_2^a$	1-Hexene	24 h	2	Hexane (97)
(43)	$CoCl_2^b$	1-Hexene	24 h	0	Hexane (97)
(44)	$NiCl_2^b$	1-Hexene	24 h	0	Hexane (97)
(45)	$TiCl_3^b$	1-Hexene	24 h	0	Hexane (96)
(46)	$FeCl_2^a$	*cis*-2-Hexene	24 h	0	Hexane (98)
(47)	$CoCl_2^b$	*cis*-2-Hexene	24 h	70	Hexane (32)
(48)	$CoCl_2^a$	*cis*-2-Hexene	24 h	0	Hexane (98)
(49)	$NiCl_2^b$	*cis*-2-Hexene	24 h	70	Hexane (28)
(50)	$NiCl_2^a$	*cis*-2-Hexene	24 h	3	Hexane (95)

Table 38. (Continued)

Exp.	Metal Halide	Alkene Substrate	Reaction Condition	Substrate Recovery (%)	Alkane Yield (%)
(51)	$TiCl_3$[b]	cis-2-Hexene	24 h	80	Hexane (18)
(52)	$FeCl_2$[a]	trans-2-Hexene	24 h	0	Hexane (99)
(53)	$CoCl_2$[a]	trans-2-Hexene	24 h	0	Hexane (96)
(54)	$NiCl_2$[a]	trans-2-Hexene	24 h	0	Hexane (95)
(55)	$TiCl_3$[a]	trans-2-Hexene	24 h	10	Hexane (90)
(56)	$FeCl_3$[a]	2-Ethyl-1-hexene	24 h 48 h	20 0	3-Methylheptane (80) 3-Methylheptane (95)
(57)	$CoCl_2$[b]	2-Ethyl-1-hexene	48 h	--	3-Methylheptane (35)
(58)	$CoCl_2$[a]	2-Ethyl-1-hexene	24 h	0	3-Methylheptane (98)
(59)	$NiCl_2$[b]	2-Ethyl-1-hexene	48 h	--	3-Methylheptane (15)
(60)	$NiCl_2$[a]	2-Ethyl-1-hexene	24 h 48 h	18 0	3-Methylheptane (82) 3-Methylheptane (95)
(61)	$TiCl_3$[b]	2-Ethyl-1-hexene	48 h	--	3-Methylheptane (10)
(62)	$TiCl_3$[a]	2-Ethyl-1-hexene	24 h 48 h	10 2	3-Methylheptane (88) 3-Methylheptane (94)

Table 38. (Continued)

Exp.	Metal Halide	Alkene Substrate	Reaction Condition	Substrate Recovery (%)	Alkane Yield (%)
(63)	$FeCl_2$[a]	Cyclohexene	24 h	0	Cyclohexane (96)
(64)	$CoCl_2$[b]	Cyclohexene	48 h	45	Cyclohexane (55)
(65)	$CoCl_2$[a]	Cyclohexene	24 h	0	Cyclohexane (96)
(66)	$NiCl_2$[b]	Cyclohexene	48 h	60	Cyclohexane (40)
(67)	$NiCl_2$[a]	Cyclohexene	24 h	2	Cyclohexane (94)
(68)	$TiCl_3$[b]	Cyclohexene	48 h	95	Cyclohexane (0)
(69)	$TiCl_3$[a]	Cyclohexene	24 h 48 h	60 0	Cyclohexane (45) Cyclohexane (95)

a. The molar ratio of $LiAlH_4$:metal halide:alkene is 1.0:1.0:2.0.

b. The molar ratio of $LiAlH_4$:metal halide:alkene is 1.0:0.1:2.0.

Table 39. Reactions of Phenylethyne with $LiAlH_4$-Transition Metal Halides

Exp.	Metal Halide	Molar Ratio $LiAlH_4$:Metal Halide:Substrate	Reaction Condition	Phenylethyne Recovery (%)	Styrene (%)	Ethylbenzene (%)
(70)	VCl_3	1:1:3.5	0.5 h	92	5	2
			3 h	50	21	13
			24 h	7	40	20
(71)	VCl_3	1:1:2	1 h	88	11	5
			24 h	0	71	32
(72)	$CrCl_3$	1:1:3.5	0.5 h	19	33	27
(73)	$CrCl_3$	1:1:2	1 h	0	25	62
			24 h	0	7	74
(74)	$MnCl_2$	1:1:3.5	3 h	53	38	8
			24 h	0	21	53
(75)	$FeCl_2$	1:1:3.5	0.5 h	0	37	35
(76)	$FeCl_2$	1:1:2	1 h	0	14	68
			24 h	0	~1	85
(77)	$FeCl_2$	1:1:2	-40°C,10 min.	~0	92	~0
(78)	$FeCl_2$	1:1:1	10 min.	0	10	86
			24 h	0	0	94
(79)	$FeCl_3$	1:1:3.5	0.5 h	0	37	51

Table 39. (Continued)

Exp.	Metal Halide	Molar Ratio $LiAlH_4$:Metal Halide:Substrate	Reaction Condition	Phenylethyne Recovery (%)	Styrene (%)	Ethylbenzene (%)
(80)	$FeCl_3$	1:1:2	1 h	0	10	56
			24 h	0	~1	72
(81)	$CoCl_2$	1:0.1:3.5	24 h	10	63	13
(82)	$CoCl_2$	1:0.1:2.0	-40°C,10 min.	55	35	8
			RT 24 h	15	60	21
(83)	$NiCl_2$	1:0.1:3.5	0.5 h	0	86	~5
			3 h	0	77	16
			24 h	0	62	26
(84)	$NiCl_2$	1:0.1:2	1 h	0	55	45
(85)	$NiCl_2$	1:0.1:2	-40°C,10 min.	32	62	0
			-40°C,30 min.	10	88	0
			-40°C,60 min.	~0	94	0
			RT 24 h	0	35	65
(86)	$NiCl_2$	1:0.1:1	10 min.	0	45	52
			24 h	0	0	99
(87)	$TiCl_3$	1:0.1:2	24 h	42	34	5

Table 40. Reactions of Diphenylethyne with $LiAlH_4$-Transition Metal Halides

Exp.	Metal Halide	Molar Ratio $LiAlH_4$:Metal Halide:Substrate	Reaction Condition	Stilbene cis	Stilbene trans	1,2-diphenylethane
(88)	VCl_3	1:1:1	24 h	26	33	13
(89)	$CrCl_3$	1:1:1	24 h	10	47	37
(90)	$MnCl_2$	1:1:1	24 h	15	6	2
(91)	$FeCl_3$	1:1:1	24 h	17	0	81
(92)	$FeCl_2$	1:1:1	24 h	8	8	79
(93)	$FeCl_2$	1:1:1	-40°C,1 h	42	0	6
(94)	$FeCl_2$	1:1:4	-40°C,1 h	12	0	0
			RT,3 h	86	0	5
(95)	$CoCl_2$	1:0.1:1	24 h	14	14	7
(96)	$CoCl_2$	1:0.1:1	-20°C,4 h	24	0	0
			RT,24 h	18	10	~0
(97)	$CoCl_2$	1:1:1	-40°C,1 h	50	trace	35
(98)	$CoCl_2$	1:1:4	-20°C,1 h	52	4	0
			RT,12 h	72	12	5
(99)	$NiCl_2$	1:0.1:1	24 h	13	16	5

Table 40. (Continued)

Exp.	Metal Halide	Molar Ratio $LiAlH_4$:Metal Halide:Substrate	Reaction Condition	Stilbene cis	Stilbene trans	1,2-diphenylethane
(100)	$NiCl_2$	1:0.1:1	-20°C,4 h	8	0	0
			RT,24 h	75	0	15
(101)	$NiCl_2$	1:1:1	-40°C,1 h	23	0	52
(102)	$NiCl_2$	1:1:4	-20°C,1 h	40	0	0
			RT,12 h	75	4	5
(103)	$TiCl_3$	1:0.1:1	24 h	25	9	18
(104)	$TiCl_3$	1:1:1	-40°C,1 h	0	0	0

Table 41. Reactions of Other Alkynes with $LiAlH_4$-Transition Metal Halides

Exp.	Metal Halide	Alkyne Substrate	Reaction Condition	Products (%)		
(105)	$FeCl_2$[a]	1-Octyne	-40°C, 10 min.	1-Octene (80), Octane (16)		
			-40°C, 1 h	1-Octene (60), Octane (37)		
			RT, 48 h	1-Octene (0) , Octane (98)		
(106)	$CoCl_2$[b]	1-Octyne	-40°C, 1 h	1-Octene (70), Octane (17)		
			RT, 48 h	1-Octene (73), Octane (23)		
(107)	$NiCl_2$[b]	1-Octyne	-40°C, 1 h	1-Octene (96), Octane (1)		
			RT, 48 h	1-Octene (99), Octane (1)		
				2-Hexene		Hexane
				Cis	Trans	
(108)	$FeCl_2$[a]	2-Hexyne	-40°C, 1 h	(55)	(11)	(4)
			RT, 2 h	(16)	(14)	(63)
(109)	$CoCl_2$[b]	2-Hexyne	RT, 2 h	(40)	(5)	(4)
			RT, 48 h	(82)	(4)	(6)
(110)	$CoCl_2$[a]	2-Hexyne	-40°C, 1 h	(32)	(62)	(0)
			RT, 24 h	(12)	(18)	(62)
(111)	$NiCl_2$[b]	2-Hexyne	RT, 2 h	(40)	(0)	(6)
			RT, 24 h	(91)	(0)	(4)
(112)	$NiCl_2$[a]	2-Hexyne	-40°C, 1 h	(85)	(0)	(3)
			-40°C, 2 h	(92)	(0)	(5)
			RT, 24 h	(18)	(20)	(58)

a,b: See notes in Table 38.

Table 42. Reduction of Halides by $LiAlH_4$-Transition Metal Chlorides at Room Temperature, in THF Solvent[1]

Exp.	Halide[4] Substrate	Transition Metal Chloride (2)	Reaction Time	Product(s) & Yield(s)	
(113)	1-Chlorodecane[5]	none	24 h	*n*-Decane	(68)
(114)	1-Chlorodecane[5]	VCl_3	24 h	*n*-Decane	(75)
(115)	1-Chlorodecane[5]	$CrCl_3$	24 h	*n*-Decane	(90)
(116)	1-Chlorodecane[5]	$MnCl_2$	24 h	*n*-Decane	(19)
(117)	1-Chlorodecane[5]	$FeCl_3$	24 h	*n*-Decane	(100)
(118)	1-Chlorodecane[5]	$FeCl_2$	24 h	*n*-Decane	(95)
(119)	1-Chlorodecane[5]	$FeCl_2$[3]	24 h	*n*-Decane	(85)
(120)	1-Chlorodecane[5]	$CoCl_2$[3]	24 h	*n*-Decane	(100)
(121)	1-Chlorodecane[5]	$NiCl_2$[3]	24 h	*n*-Decane	(100)
(122)	1-Chlorodecane[5]	$TiCl_2$[3]	24 h	*n*-Decane	(100)
(123)	1-Bromodecane[5]	none	1 h	*n*-Decane	(92)
(124)	1-Bromodecane[5]	VCl_3	1 h	*n*-Decane	(40)

Table 42. (Continued)

Exp.	Halide[4] Substrate	Transition Metal Chloride (2)	Reaction Time	Product(s) & Yield(s)	
(125)	1-Bromodecane[5]	$CrCl_3$	1 h	n-Decane	(65)
(126)	1-Bromodecane[5]	$MnCl_2$	1 h	n-Decane	(43)
(127)	1-Bromodecane[5]	$FeCl_3$	1 h	n-Decane	(50)
(128)	1-Bromodecane[5]	$FeCl_2$	1 h	n-Decane	(100)
(129)	1-Bromodecane[5]	$FeCl_2$[3]	1 h	n-Decane	(90)
(130)	1-Bromodecane[5]	$CoCl_2$	1 h	n-Decane	(98)
(131)	1-Bromodecane[5]	$CoCl_2$[3]	1 h	n-Decane	(98)
(132)	1-Bromodecane[5]	$NiCl_2$	1 h	n-Decane	(100)
(133)	1-Bromodecane[5]	$NiCl_2$[3]	1 h	n-Decane	(100)
(134)	1-Bromodecane[5]	$TiCl_3$	1 h	n-Decane	(96)
(135)	1-Bromodecane[5]	$TiCl_3$[3]	1 h	n-Decane	(98)
(136)	1-Iododecane	none	1 h	n-Decane	(98)
(137)	1-Iododecane	$FeCl_2$	1 h	n-Decane	(98)

Table 42. (Continued)

Exp.	Halide[4] Substrate	Transition Metal Chloride (2)	Reaction Time	Product(s) & Yield(s)	
(138)	1-Iododecane	$CoCl_2$[3]	1 h	*n*-Decane	(98)
(139)	1-Iododecane	$NiCl_2$[3]	1 h	*n*-Decane	(98)
(140)	1-Iododecane	$TiCl_3$[3]	1 h	*n*-Decane	(100)
(141)	1-Fluorodecane	none	24 h	*n*-Decane	(0)
(142)	1-Fluorodecane	$FeCl_2$	24 h	*n*-Decane	(16)
(143)	1-Fluorodecane	$CoCl_2$[3]	24 h	*n*-Decane	(10)
(144)	1-Fluorodecane	$NiCl_2$[3]	24 h	*n*-Decane	(7)
(145)	1-Fluorodecane	$TiCl_3$[3]	24 h	*n*-Decane	(9)
(146)	n-Octyltosylate	none	24 h	*n*-Octane	(92)
(147)	n-Octyltosylate	$FeCl_2$	24 h	*n*-Octane	(25)
(148)	n-Octyltosylate	$CoCl_2$[3]	24 h	*n*-Octane	(100)
(149)	n-Octyltosylate	$NiCl_2$[3]	24 h	*n*-Octane	(98)
(150)	n-Octyltosylate	$TiCl_3$[3]	24 h	*n*-Octane	(54)

Table 42. (Continued)

Exp.	Halide[4] Substrate	Transition Metal Chloride (2)	Reaction Time	Product(s) & Yield(s)	
(151)	3-Bromooctane	none	24 h	*n*-Octane	(75)
(152)	3-Bromooctane	$FeCl_2$	24 h	*n*-Octane	(90)
(153)	3-Bromooctane	$CoCl_2$	24 h	*n*-Octane	(98)
(154)	3-Bromooctane	$NiCl_2$	24 h	*n*-Octane	(92)
(155)	3-Bromooctane	$TiCl_3$	24 h	*n*-Octane	(88)
(156)	Bromocyclohexane	none	24 h	Cyclohexane	(0)
(157)	Bromocyclohexane	$FeCl_2$	24 h	Cyclohexane	(97)
(158)	Bromocyclohexane	$CoCl_2$	24 h	Cyclohexane	(99)
(159)	Bromocyclohexane	$NiCl_2$	24 h	Cyclohexane	(99)
(160)	Bromocyclohexane	$TiCl_3$	24 h	Cyclohexane	(100)
(161)	Chlorocyclohexane	none	24 h	Cyclohexane	(0)
(162)	Chlorocyclohexane	$FeCl_2$	24 h	Cyclohexane	(98)
(163)	Chlorocyclohexane	$CoCl_2$	24 h	Cyclohexane	(92)

Table 42. (Continued)

Exp.	Halide[4] Substrate	Transition Metal Chloride (2)	Reaction Time	Product(s) & Yield(s)	
(164)	Chlorocyclohexane	$CoCl_2$[3]	24 h	Cyclohexane	(3)
(165)	Chlorocyclohexane	$NiCl_2$	24 h	Cyclohexane	(95)
(166)	Chlorocyclohexane	$NiCl_2$[3]	24 h	Cyclohexane	(5)
(167)	Chlorocyclohexane	$TiCl_3$	24 h	Cyclohexane	(95)
(168)	Chlorocyclohexane	$TiCl_3$[3]	24 h	Cyclohexane	(95)
(169)	1-Bromoadamantane	none	24 h	Adamantane	(70)
(170)	1-Bromoadamantane	$FeCl_2$	24 h	Adamantane	(100)
(171)	1-Bromoadamantane	$CoCl_2$	24 h	Adamantane	(100)
(172)	1-Bromoadamantane	$NiCl_2$	24 h	Adamantane	(100)
(173)	1-Bromoadamantane	$TiCl_3$[3]	24 h	Adamantane	(100)
(174)	Chlorobenzene	none	24 h	Benzene	(0)
(175)	Chlorobenzene	$FeCl_2$	24 h	Benzene	(72)
(176)	Chlorobenzene	$CoCl_2$	24 h	Benzene	(25)

Table 42. (Continued)

Exp.	Halide Substrate[4]	Transition Metal Chloride (2)	Reaction Time	Product(s) & Yield(s)	
(177)	Chlorobenzene	$CoCl_2$[3]	24 h	Benzene	(0)
(178)	Chlorobenzene	$NiCl_2$	24 h	Benzene	(100)
(179)	Chlorobenzene	$NiCl_2$[3]	24 h	Benzene	(0)
(180)	Chlorobenzene	$TiCl_3$[3]	24 h	Benzene	(45)
(181)	Bromobenzene	none	24 h	Benzene	(0)
(182)	Bromobenzene	$FeCl_2$	24 h	Benzene	(80)
(183)	Bromobenzene	$CoCl_2$	24 h	Benzene	(74)
(184)	Bromobenzene	$CoCl_2$[3]	24 h	Benzene	(23)
(185)	Bromobenzene	$NiCl_2$	24 h	Benzene	(100)
(186)	Bromobenzene	$NiCl_2$[3]	24 h	Benzene	(87)
(187)	Bromobenzene	$TiCl_3$[3]	24 h	Benzene	(91)
(188)	Iodobenzene	none	24 h	Benzene	(38)
(189)	Iodobenzene	$FeCl_2$	24 h	Benzene	(98)

Table 42. (Continued)

Exp.	Halide Substrate[4]	Transition Metal Chloride (2)	Reaction Time	Product(s) & Yield(s)	
(190)	Iodobenzene	$CoCl_2$	24 h	Benzene	(98)
(191)	Iodobenzene	$NiCl_2$	24 h	Benzene	(100)
(192)	Iodobenzene	$TiCl_3$[3]	24 h	Benzene	(92)

(1) All reactions are carried out at -78°C for 10 minutes, then warmed to room temperature by removing the cooling bath. The reaction time was counted beginning with the period at -78°C. Yields were determined by glc using suitable internal standard.

(2) Molar ratio of $LiAlH_4$ to transition metal chloride is 1:1, except when noted.

(3) 10% molar equivalent

(4) Halide substrate was used in equivalent molar amount to $LiAlH_4$ except when noted.

(5) Halide substrate was in half equivalent to $LiAlH_4$.

Table 43. Deuterium Experiments in Reactions of 1-Octene with $LiAlH_4$-Transition Metal Halide

Transition Metal Halide	Molar Ratio of $LiAlH_4$:Metal Halide	Reaction Condition	Octane Yield (%)	Deuterium Incorporation (%)
$FeCl_2$	1.0:1.0	0°C, 1 h	100	26
		RT, 24 h	100	25
$CoCl_2$	1.0:0.10	RT, 24 h	100	12
$NiCl_2$	1.0:0.10	RT, 24 h	100	14
$NiCl_2$	1.0:1.0	RT, 24 h	100	13
$TiCl_3$	1.0:0.10	RT, 24 h	100	94
$NiCl_2(Ph_3P)_2$	1.0:0.10	RT, 24 h	45	37
$NiCl_2(Ph_3P)_2$	1.0:0.20	RT, 24 h	80	42
$CpNiCl(Ph_3P)_2$	1.0:0.10	RT, 24 h	85	27
$(COD)_2Ni(Ph_3P)_2$	1.0:0.10	RT, 24 h	95	47

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PART VI

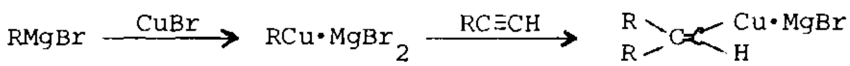
SELECTIVE REDUCTION OF ALKYNES BY MgH_2-CuI AND MgH_2-CuO-*t*-Bu

CHAPTER I

INTRODUCTION

Background

Organocopper reagents such as the Normant reagent add to unactivated primary terminal acetylenes[1,2] (reaction 1). Recently, Crandall reported that the reduction of disubstituted acetylenes to the corres-



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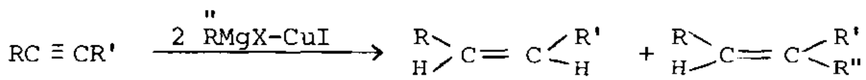
ponding cis olefins has been effected by an organocopper reagent prepared from CuI and 2 equivalents of a primary Grignard reagent.[3] These reactions are potentially important because of their stereospecificity and



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(2)

versatility in organic synthesis.[4-9] However, the main reduction product **1** was accompanied by a side alkylation product **2**. In our laboratories, a very active form of HgH_2 has been made. The combination of MgH_2 and CuI might solve the reported problem of side product reaction.

Purpose

To study the reactivity and stereochemistry of the reaction of MgH_2-CuI with alkynes is the purpose of this study.

CHAPTER II

EXPERIMENTAL

General Considerations

Techniques for handling air-sensitive compounds, apparatus and instruments are the same as previously described in the experimental sections of Part I and Part II.

Materials

Diphenylethyne, phenylethyne, 2-hexyne, 1-octyne, 1-octene (Chemical Sample Company) and 1-hexyne (Beacon Chemical Industries, Inc.) were purchased commercially and used without further purification.

The sources of CuI and MgH_2 are the same as described in Part I and Part IV, respectively.

Preparation of Cuprous tert-Butoxide[10]

50 mmoles of BuLi in n-hexane added dropwise to a solution of tert-butanol (50 mmoles) in THF and was stirred for 1 hour. This solution (containing 50 mmoles of LiOt-Bu) was added to a slurry of cuprous chloride (4.95g; 50 mmoles) in THF and stirred for another 1 hour after which the solvents were removed under vacuum. The residue was sublimed in vacuo at 160° C/0.1 mm to give yellowish crystals (yield, 70%). Anal. Found Cu:t-BuOH = 1.00:1.03.

General Reactions of MgH_2-CuI with Alkynes

The experimental procedures were similar to those described in Part I. A slurry of MgH_2 in THF was syringed into the mixture of alkyne and CuI (or CuO-t-Bu) at -78°C. Then, the temperature was allowed to increase to room temperature by removing the cooling bath; a deep black color and slight gas evolution were observed at RT. After an indicated period (24 or 48 h) the reaction mixture was quenched with distilled water, dried over $MgSO_4$, and extracted by several portions of THF. Product analyses were carried out by either NMR integration or glc with an internal standard, which have been described in Part V.

CHAPTER III

RESULTS AND DISCUSSION

Results of alkyne reduction by the reagents MgH_2-CuI or MgH_2-CuO-t-Bu are summarized in Table 44. The terminal alkynes, 1-hexyne, 1-octyne and phenylethyne, were reduced to the corresponding alkene with 100% selectivity (0% alkene) in 80-98% yield. The internal alkynes, 2-hexyne and diphenylethyne, were converted to *cis*-alkene as

$$R\text{-}C\equiv C\text{-}H \xrightarrow{\quad} \underset{80\text{-}98\%}{R\text{-}CH=CH_2} \qquad \text{(the only product)}$$

(where R = *n*-C_4H_9, *n*-C_6H_{13} or Ph)

the only product (no *trans*-alkene or alkane was detected) in 80-95% yield. The alkene, 1-octene, was not affected by both reagents.

$$R\text{-}C\equiv C\text{-}R' \xrightarrow{\qquad} \underset{80\text{-}95\%}{\overset{R}{\underset{H}{>}}C=C\overset{R'}{\underset{H}{<}}} \qquad \text{(the only product)}$$

(where R=*n*-C_4H_9, R'=CH_3 or R=R'=C_6H_5)

The high stereospecificity of the reaction of MgH_2-CuI (or CuO-t-Bu) reveals that these reagents are potentially useful in organic synthesis. According to the Normant reagent ($RCu{\cdot}MgX_2$), the intermediate of MgH_2-CuI (or O-t-Bu) might be some kind of magnesium copper hydride, presumably $HCu{\cdot}MgHX$ (X=I or O-t-Bu). However, the direct evidence for this intermediate is still absent.

CHAPTER IV

CONCLUSIONS

MgH_2-CuI (or CuO-*t*-Bu) is an excellent reagent for selective reduction of alkynes. The terminal and internal alkynes were reduced to the corresponding alkenes and *cis*-alkenes, respectively in high yield. The reaction intermediate involved in this reaction as well as the dependent of the scope of this reaction is in progress.

Table 44. Reduction of Alkynes by MgH_2-CuI or MgH_2-CuO-*t*-Bu in THF[a], at RT

Alkyne	Hydride Reagent	Reaction Time	Alkyne % Recovered	Products (%)
1-hexyne	MgH_2-CuI	48 h	0	1-hexane (80), hexane (0)
1-hexyne	MgH_2-CuO-*t*-Bu	48 h	5	1-hexane (78), hexane (0)
2-hexyne	MgH_2-CuI	48 h	0	*cis*-2-hexane (80), trans-2-hexane (0), hexane (0)
2-hexyne	MgH_2-CuO-*t*-Bu	48 h	7	*cis*-2-hexane (81), trans-2-hexane (0), hexane (0)
1-octyne	MgH_2-CuI	48 h	5	1-octene (84), octane (0)
1-octyne	MgH_2-CuO-*t*-Bu	48 h	0	1-octene (92), octane (0)
phenylethyne	MgH_2-CuI	24 h	0	styrene (98), phenylethane (0)
diphenyl-ethyne	MgH_2-CuI	24 h	0	*cis*-stibene (95), *trans*-stilbene (0), 1,2-diphenylethane (0)

a. The molar ratio of MgH_2:CuI (or CuO-*t*-Bu):Alkyne = 1.0 = 1.0:0.25.

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