Organometallic Chemistry of the Main Group Elements: Mechanisms, Stereochemistry and Transition Metal Catalysis

Project No: G-33-636

Project Director: Dr. E.C. Ashby

Sponsor: National Science Foundation, Washington, D.C. 20550

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*Includes 6 mos. flexibility period

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Defense Priority Rating: n/a

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CA-3 (3/76)
Project Title: Organometallic Chemistry of the Main Group Elements: Mechanisms, Stereochemistry and Transition Metal Catalysis
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Project Director: Dr. E.C. Ashby
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Effective Termination Date: 11/30/81
Clearance of Accounting Charges: 2/28/82

Grant/Contract Closeout Actions Remaining:

- [x] Final Invoice and Closing Documents
- [ ] Final Fiscal Report
- [x] Final Report of Inventions
- [x] Govt. Property Inventory & Related Certificate
- [ ] Classified Material Certificate
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This past year has been dedicated to working on several problems. The first problem involves the use of probes in the detection of radical intermediates in the reaction of Grignard reagents with ketones. The reaction below e.g. shows that even primary Grignard reagents react with aromatic ketones by electron transfer.

\[
\text{MgCl} + \text{Ph}_2\text{C}=\text{O} \rightarrow \frac{\text{H}_2\text{O}}{\text{H}^+} \text{Ph}_2\text{COH} + \text{Ph}_2\text{COH}
\]

This result was obtained sometime ago, but had to be verified by a new graduate student. More recently we have used this probe and other probes to establish the electron transfer nature of LiAlH}_4 in its reaction with alkyl halides and ketones.

\[
\text{I} + \text{LiAlH}_4 \rightarrow \text{THF} \rightarrow \text{pentane} + \text{alkene}
\]

\[
\text{Ph}_2\text{C}=\text{O} + \text{LiAlH}_4 \rightarrow \text{THF} \rightarrow \text{Ph}_2\text{C}=\text{O}^-
\]
These latter results are remarkable and represent a most important finding. We are presently exploiting these results as rapidly as possible.

The second problem is concerned with the determination of the composition of the Normant Reagent.

\[ RMgX + CuX \longrightarrow RCu \cdot MgX_2 \]

\[ RCu \cdot MgX_2 + R'C=CH \longrightarrow R' - C = C - H \]

\[ R \quad \text{Cu} \quad MgX_2 \]

The Normant Reagent has been represented by the empirical formula RCu · MgX₂. By variable temperature nmr studies, we have determined that RCu · MgX₂ is not formed, but rather a series of copper magnesium alkyls which do not contain halogen. The active species in the Normant Reagent responsible for addition to alkynes is Cu₂MgR₄ which adds to alkynes activated by MgX₂ via a π-complex.

The third project is concerned with reactions of Grignard reagents with CO to form acyl Grignards \((RC = MgX)\). This study is complete and will be reported in detail shortly. The reaction of acid halides with magnesium is also being studied as a route to acyl Grignard reagents. Reasonable success so far has been achieved.

\[
R - O - C - X + Mg \xrightarrow{\text{activated}} R - O - MgX \xrightarrow{-100^\circ} \text{THF} \xrightarrow{\text{substrate}} R - O - \text{substrate}
\]

And last a study has been carried out concerning the reaction of RMgH compounds with ketones. In most cases exclusive reduction takes place with a high degree of stereoselectivity. A study is also nearly complete
concerning the hydrometallation of olefins by RMgH, R₂Mg and RMgX compounds.

\[
R - Mg - H + 2RC = CH_2 \xrightarrow{Cp_2TiCl_2} (RCH₂CH₂)_₂Mg
\]
Our research sponsored by NSF over the past three years has been concerned with three major areas: (1) the mechanism of Grignard compound addition to ketones; (2) the development of new reagents to be used for various synthetic transformations and (3) the evaluation of single electron transfer as an important mechanistic pathway in organic reactions. Our efforts over the past three years have resulted in 35 publications.

We have essentially completed our work concerning the mechanism of Grignard compound addition to ketones although it seems clear that with the specific methodology we have developed, we should later on extend these studies to include aldehydes, esters and nitriles as well as RLi, R₂Zn and R₃Al compounds. We have also essentially completed our studies involving reactions with new reagents. The new reagents: LiAlH₄ - transition metal halide, higher lithium alkylcuprates, RMgH compounds, ROMgH compounds, MgH₂-CuI, MgH₂-Cp₂TiCl₂, RMgOR and RMgNR₂ compounds have been tested in various reactions and found to be very valuable reagents for certain transformations. Our evaluation of reactions of MI, MR, NOR, NNIR₂ compounds as electron transfer reagents toward a variety of organic substrates (e.g., alkyl halides, ketones, etc) has provided results beyond our expectations. This work will be continued in the immediate future.

### PART III—TECHNICAL INFORMATION (FOR PROGRAM MANAGEMENT USES)

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#### 2. Principal Investigator/Project Director Name (Typed)

E.C. Ashby

#### 3. Principal Investigator/Project Director Signature

5/3/82
PUBLICATIONS (1978 through mid 1981)

The following publications are as a result of work supported by NSF.


THESIS

1. John P. Oliver

2. Robert Scott Smith
PART I. STEREOSELECTIVE ALKYLATION REACTIONS INVOLVING
METHYLMAGNESIUM ALKOXIDES

The stereoselective nature of several methyilmagnesium alkoxides, when reacting with a series of substituted cyclohexanones, was investigated. The bulky ligand attached to the magnesium enhanced the stereoselectivity of these alkylating agents over that observed with the usual Grignard reagents. Enolization was a competitive side reaction involved in these alkylations.

PART II. INVESTIGATIONS OF HALOMAGNESIUM ALKOXIDE
REDUCTION OF KETONES

Various halomagnesium alkoxides were prepared and investigated as stereoselective reducing agents. With 4-t-butylcyclohexanone the thermodynamically more stable isomer was produced in high yield. Experiments were carried out which indicated that the alcohol ratios obtained were not an artifact of equilibration. These Meerwein-Pondorf-Verley type reductions were carried out in various solvents under different conditions to obtain product ratios and optimum reaction conditions. The almost exclusive mode of attack was from the axial side and appears to be an inherent property of these reagents. Aldol condensation leading to undesired by-product did not detract from the high stereoselectivity.
Camphor and norcamphor were not reduced to any significant extent by these reagents nor was 3,3,5-trimethylcyclohexanone. 2-Methylcyclohexanone also yielded poor stereochemical and stoichiometric results.

PART III. STEREOSELECTIVE REACTIONS OF COMPLEX METAL HYDRIDES AND TRIALKYL ALUMINUM COMPOUNDS WITH KETONES

Stereoselective alkylation and reduction reactions were carried out on the following diagnostic ketones: 2-methylcyclohexanone, 4-t-butylcyclohexanone, cis and trans-2-methyl-4-t-butylcyclohexanone, cis,cis and cis,trans-2,6-dimethyl-4-t-butylcyclohexanone. The ketones were alkylated with Grignard reagents and with trimethylaluminum in both 1:1 and 3:1 ratio. Reductions of the ketones were carried out using triisobutyl aluminum hydride, lithium aluminum hydride, chloromagnesium aluminum hydride, magnesium aluminum hydride and aluminum hydride.

For the series of complex metal hydrides, reduction of anchored and, therefore, conformationally stable 4-t-butylcyclohexanones yielded relatively constant axial to equatorial alcohol ratios as the result of torsional versus steric strain. The results are dictated by steric factors in the substrate molecule. Complexation of the carbonyl with a cation or other Lewis base caused a conformational change in the unanchored 2-methylcyclohexanone as reflected in results differing from the other diagnostic ketones.

Analysis of the data obtained from the alkylation reactions indicated that the Grignard reagent is generally smaller than trimethylaluminum when the aluminum alkyl reacts in 1:1 ratio with ketone. Analysis of the transition state energies for lithium aluminum hydride.
reductions indicated that the Grignard is the more bulky species. When used in excess the trimethylaluminum reaction results are explained on the basis of the compression effect. Differences in transition state energies were used to arrive at a semi-quantitative value of the compression effect. Using 4-t-butylcyclohexanone as the parent ketone relative values for excess destabilization energies were calculated for the other diagnostic ketones. This excess destabilization energy reflects itself in the compression strain energy which causes the reversal of the axial to equatorial product ratio when trimethylaluminum is used in 3:1 ratio with ketone.
ELECTROPHILIC CLEAVAGE OF MAIN GROUP ORGANOMETALLIC COMPOUNDS BY CARBONYL ELECTROPHILES

A THESIS
Presented to
The Faculty of Division of Graduate Studies
By
R. Scott Smith

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy in the School of Chemistry

Georgia Institute of Technology
May 1980
Part I. Electron Transfer Participation in the Reactions of Grignard Reagents with Ketones

Competition experiments involving the reaction of a ketone with two different Grignard reagents and a Grignard reagent with two different ketones were carried out for a series of ketones and Grignard reagents. The steric and electronic properties of both the ketones and Grignard reagents were varied in order to determine whether a polar or electron transfer (ET) mechanism is in effect. For the biaryl ketones studied, the results of the competition experiments are consistent only with an ET mechanism. Conversely, acetone was found to react exclusively by a polar mechanism with all the Grignard reagents studied. We have concluded that the major factor determining whether or not ET occurs in these reactions is the stability of the ketyl intermediate. In this regard, acetophenone was found to be on the borderline for ketyl stability necessary for ET to occur. Steric hinderance, especially due to branching at the β-carbon of the Grignard reagent was found to influence the rate determining step involving alkylations by the ET mechanism. A mechanistic scheme is presented that defines different rate determining steps for ET reactions of primary and secondary or tertiary alkyl Grignard reagents. In addition, the method and results should be applicable to identifying ET steps in the electrophilic cleavage of other alkyl metal compounds.
Part II. The Nature of the Transition State in the Reaction of Trialkylaluminum Compounds With Ketones

Because of the stereochemical significance of the reaction of trialkylaluminum compounds with substituted cyclohexanones in 2:1 ratio in benzene, an attempt was made to more clearly define the nature of the transition state involved in this reaction. In this connection, molecular weight and NMR studies were carried out in hydrocarbon solvents on the systems \((\text{CH}_3)_3\text{Al-O(C}_2\text{H}_5)_2\), \((\text{CH}_3)_2\text{Al-Ph}_2\text{C}=0\) and \((\text{CH}_3)_2\text{AlCl-Ph}_2\text{C}=0\) in an attempt to observe an intermediate that would reflect the transition state structure. In addition, \(\text{Et}_2\text{AlCH}_2\text{AlEt}_2\) (I) was allowed to react with 4-tert-butylcyclohexanone in hydrocarbon solvent at different molar ratios as a mechanistic probe that would constrain two aluminum atoms to a bridging configuration in the transition state. The results support the importance of a bridging alkyl group described in the formation of a six centered transition state for the reaction of two equivalents of a trialkylaluminum compound with a ketone in hydrocarbon solvent. The results also argue against any significant contribution from a transition state described by two moles of trialkylaluminum compound complexed to the carbonyl oxygen atom.

As a precondition for the use of (I) as a mechanistic probe (I) was prepared in benzene and the solution composition determined. The addition of one molar equivalent of diethyl ether to this mixture formed a substitution labile etherate, \(\text{Et}_2\text{AlCH}_2\text{AlEt}_2 \cdot \text{OEt}_2\). Low temperature 

\(^1\text{H} \text{nmr data indicates that the ether oxygen is simultaneously coordinated}
to both aluminum atoms. In addition to (I), Me₂AlCH₂AlMe₂ (II) was synthesized in diethyl ether solvent, but could not be synthesized in hydrocarbon solvent. Attempts to synthesize (II) from Cl₂AlCH₂AlCl₂ and dimethylzinc in toluene led to the formation ClZnCH₂ZnCl.

Part III. Concerning the Preparation of Acyl Grignard Reagents

An attempt was made to prepare an acyl Grignard reagent by two different methods. The first method involved the carbonylation of hindered aryl Grignard reagents. While this method did not produce a stable acyl Grignard reagent, the presence of unreacted aryl Grignard reagent was identified as the major contributing factor to its instability. The results are best rationalized by an electron transfer from aryl Grignard reagent to the intermediate acyl Grignard reagent. The second method involved the reaction of an acid halide with magnesium metal, a reaction which has not been previously reported. While this method holds promise for the formation of acyl Grignard reagents, severe problems still need to be solved.