INFORMATION TO USERS

This was produced from a copy of a document sent to us for microfilming. While the most advanced technological means to photograph and reproduce this document have been used, the quality is heavily dependent upon the quality of the material submitted.

The following explanation of techniques is provided to help you understand markings or notations which may appear on this reproduction.

1. The sign or “target” for pages apparently lacking from the document photographed is “Missing Page(s)”. If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting through an image and duplicating adjacent pages to assure you of complete continuity.

2. When an image on the film is obliterated with a round black mark it is an indication that the film inspector noticed either blurred copy because of movement during exposure, or duplicate copy. Unless we meant to delete copyrighted materials that should not have been filmed, you will find a good image of the page in the adjacent frame.

3. When a map, drawing or chart, etc., is part of the material being photographed the photographer has followed a definite method in “sectioning” the material. It is customary to begin filming at the upper left hand corner of a large sheet and to continue from left to right in equal sections with small overlaps. If necessary, sectioning is continued again—beginning below the first row and continuing on until complete.

4. For any illustrations that cannot be reproduced satisfactorily by xerography, photographic prints can be purchased at additional cost and tipped into your xerographic copy. Requests can be made to our Dissertations Customer Services Department.

5. Some pages in any document may have indistinct print. In all cases we have filmed the best available copy.
SWINDELL, CHARLES STERLING

APPLICATION OF THE FELKIN REACTION; NICKEL-INDUCED
CONVERSION OF CARBON-OXYGEN INTO CARBON-CARBON BONDS

Rice University

University Microfilms International
300 N. Zeeb Road, Ann Arbor, MI 48106

Copyright 1980
by
Swindell, Charles Sterling
All Rights Reserved
RICE UNIVERSITY

APPLICATION OF THE FELKIN REACTION; NICKEL-INDUCED CONVERSION OF CARBON-OXYGEN INTO CARBON-CARBON BONDS

by

CHARLES STERLING SWINDELL

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

DOCTOR OF PHILOSOPHY

APPROVED, THESIS COMMITTEE:

E. Wenkert, Professor
Chairman

E.S. Lewis, Professor

J.W. Hightower, Professor

HOUSTON, TEXAS
MAY, 1980
To my wife, Deborah and my parents
Abstract

The bis(triphenylphosphine)nickel dichloride-catalyzed reaction of 1-vinylcyclohexanol with phenylmagnesium bromide produced 1-phenyl-1-vinylcyclohexane as the major product. An analogous product was obtained with 1-hexynylmagnesium bromide and this allylic alcohol, while the employment of trimethylsilylethylnylmagnesium bromide led to substitution at the opposite terminus of the allyl system, yielding trimethylsilylethynylethylvilidenehexahexane. Vinylmagnesium bromide initiated a disproportionation reaction of 1-vinylcyclohexanol which was investigated through deuterium labeling experiments. An intramolecular variation of these reactions was carried out with A yielding tricycles B. Indolylmagnesium halides could be involved in these reactions as exemplified by the conversion of indolylmagnesium iodide to 3-allylindole in the presence of allyl alcohol, and to C and D in the presence of dimethylallyl alcohol. A reaction between skatole-derived Grignard
reagent and allyl alcohol led to 2-allyl-3-methylindole. The nickel-catalyzed reaction of phenylmagnesium bromide with cyclohex-2-en-1-ol and 1-isopropenylcyclohexanol yielded 1-phenyl-cyclohex-2-ene and 1-phenyl-1-isopropenylcyclohexane, respectively. Both methylmagnesium, and phenylmagnesium bromides reacted with 1,3-dimethylcyclohex-2-en-1-ol to produce largely bi-1,3-dimethylcyclohexenyl. In a nickel catalyzed reaction of methylmagnesium and phenylmagnesium bromides with E, 1-isopropenylcyclohexanol and F were produced, respectively. Nickel-cata-

![Chemical Structures](image)

lyzed substitution of the alkoxy groups of 1-methoxycyclohexene, 1-methoxy-4-tert-butylcyclohexene, 4-methoxyheptene, 1-methoxyheptene, dihydropyran, and 2-methoxynaphthalene by the alkyl or aryl groups of Grignard reagents could also be effected. Enamines, enolates, and highly hindered enol ethers proved ineffective in the latter process. An analysis of the stereochemistry associated with these substitutions revealed the original enol ether stereochemistry to be retained in most cases. A catalytic cycle explaining the enol ether substitution process is proposed.
Acknowledgements

I would like to express my sincere appreciation to Jean-Marie Bernassau, Timothy D.J. Halls, Muppala S. Raju, and Richard L. Stephens for the measurement and assignment of the $^{13}$C NMR spectra, to Thomas Arrhenius for running errands in my absence, to my wife, Deborah, for typing the manuscript and performing countless other jobs, and finally, to Prof. E. Wenkert, without whom this work would not have been possible.
Introduction

An investigation into the nickel-catalyzed reaction of Grignard reagents and allylic alcohols leading to olefins is to be made. In particular, the feasibility of hybridization changes in the Grignard reagent is to be evaluated as is the use of the novel Grignard reagents, the indolylmagnesium halides. Conducting the reaction in an intramolecular fashion will be attempted. Furthermore, structural parameters of the allylic alcohols important to the success of the reaction are to be defined through the variation of substitution patterns in these components. Finally, the involvement of allylic alcohols in this reaction with heteroatoms appended to the double bonds will be attempted.
Table of Contents

Abstract.........................................................iv
Acknowledgements...........................................vi
Introduction..................................................vii
Historical.....................................................1
Discussion......................................................52
Experimental..................................................87
Summary.......................................................123
References.....................................................125
Historical

Nucleophilic substitution reactions carried out on allylic systems have been historically of interest in organic chemistry. Roberts, Young, and Weinstein,\(^1\) for example, found in 1942 that crotol chloride, \(1\), was susceptible to displacement by acetate and ethoxide giving crotol acetate, \(2\), and crotol alcohol ethyl ether, \(3\), respectively (scheme 1). For the synthetic organic chemist, displacement reactions on allylic systems brought about by carbon nucleophiles have been a mainstay in the collection of methods exploited for carbon network construction. One of the earliest terpene synthesis schemes devised by Ruzicka,\(^2\) and later exploited by Isler, et al.\(^3\) employed the conversion of acetone, \(4\), to prenyl bromide, \(6\), through vinylisopropanol, \(5\), followed by displacement of the bromide of \(6\) by the carbon nucleophile derived from ethyl acetoacetate, \(7\). Hydrolysis, decarboxylation of the alkylation product, \(8\), led to ketone, \(2\), which was subjected to the initial sequence of operations eventually yielding nerolidol, \(11\) (scheme 2).
While the above examples amply demonstrate the utility of and interest in nucleophilic substitution reactions on allylic systems, both examples serve to underline the fact that these reactions have been largely restricted to cases in which the allylic leaving group is a relatively good one, e.g. halide above. More recently, however, several approaches to direct substitution on allylic alcohol structures have appeared in which the net result is the "one-pot" replacement of the hydroxyl function by a carbon nucleophile. Such reactions are of
interest in synthesis because the allylic alcohol substrates need not be converted to intermediates with better leaving groups, such as halides as in the above conversion of 5 to 6. Thus one step in the overall conversion of allylic alcohols to substituted derivatives may be deleted.

An early approach to such an allylic alcohol substitution reaction was reported by Nazarov, et al. in 1958. This scheme involved heating an allylic alcohol

Scheme 3

\[
5 + \text{CO}_2\text{Et} \xrightarrow{200^\circ C} 12
\]

and ethyl acetoacetate under rather drastic conditions to obtain alkylated and decarboxylated product. The interaction of vinylisopropanol, 5, and ethyl acetoacetate under these conditions led to olefinic ketone, 12, a key intermediate in Nazarov's acyclic sesquiterpene synthesis.

A related approach to allyl alcohol alkylation of ketones at high temperatures and over a solid catalyst has been described. In addition, the direct alkylation of 2-methyl-1,3-cyclopentanedione at C2 by allyl alcohol has been reported.

Salomon and Kochi found that treatment of either of the epimeric tert-butylvinylcyclohexanols, 13, 14
with trimethylaluminum in the presence of a catalytic amount of water gave an identical product distribution in which the predominant product in both instances was the tert-butylpropylidenecyclohexane, 15. In contrast,

Scheme 4

they found that under similar conditions, allylic isomer 18 of the above alcohols gave mainly 16, a quaternary carbon containing structure (scheme 4).

A general scheme for allylic alcohol substitution was reported by Mukaiyama, et al. and involved sequential reaction of the alcohol with N-alkyl-2-fluoropyridinium salt 20, followed by addition of a Grignard reagent in one pot (scheme 5). Evidently, ether 25 functioned as the intermediate which activated the allylic system toward substitution by the Grignard reagent. It is interesting to note that in the formation of 21, predominant
SN2' replacement of the hydroxyl led to formation of products in which the double bond was less substituted and the allylic carbon was more highly substituted.

In another report, Murahashi, et al. described an additional procedure of general applicability for displacement of allyl alcohol hydroxyl groups which involved treatment of the lithium salt of the alcohol with cuprous
iodide, an organolithium reagent and finally salt 32 (scheme 6). It was suggested that initially formed

Scheme 6

Yield (%) 

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Compound</th>
<th>Yield</th>
<th>Yield</th>
<th>Reaction</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
alkoxy-cuprate, 39, reacted with salt, 32, to give an intermediate, 40, which collapsed to the alkylated allyl system (scheme 7). This process seemed to produce SN2-type replacement of the hydroxyl function, as was evident particularly in the conversion of 37 to 38.

Scheme 7

\[ 32 + \text{ROCuR}_3^3\text{Li}_3 \rightarrow (\text{ROPPh}_3)^+ (\text{R}_3^3\text{CuN(Me)PhLi}_2)^- \]

\[ \rightarrow \text{R-R'} + \text{Ph}_3\text{PO} + \text{R}_3^3\text{CuN(Me)PhLi}_2 \]

In a second report, Murahashi, et al., 10 described a reversal of regiochemistry of the above reaction brought about by a structural change in the salt. Using basically the same procedure as before, except for the employment of salt 44, these workers were now able to produce SN2' substitution of structurally diverse allyl alcohols (scheme 8). This feature was most readily seen in the comparison of the two conversions 9,10 of 31 into 33 and 34 (schemes 6,8) through the agency of the respective salts and served to point out the utility of such a scheme for construction of quaternized, allylic carbons. The SN2' nature of the process was established by the conversion of allylic alcohols 45 and 47 into methylated olefins 46 and 48, respectively (scheme 9). The reactions also served to reveal the anti nature of the hydroxyl group replacement.
A reaction which involved a substitution of the allyl hydroxy function brought about by rhodium was reported in 1971. Treatment of allyl alcohol, \( 49 \), with \( \text{RhCl}_2 \cdot 3\text{H}_2\text{O} \) led to complex \( 50 \) in which the alcohol function of one allyl alcohol molecule had undergone substitution by the central carbon of another (scheme 10). An intermediate such as \( 51 \) was suggested.
Scheme 10

\[ \text{HO} + \text{RhCl}_3 \cdot 3\text{H}_2\text{O} \rightarrow \text{Cl}_2\text{RhCl}_2(\text{Cl}) \]

\[ \text{[Rh]} \]

\[ \text{OH} \]

Other transition metal-mediated substitutions on allyl alcohol included the Rh-Co or Rh-Ni catalyzed transformation into anhydrides 52 and 53 in the presence of carbon monoxide (scheme 11).\textsuperscript{12} The palladium-catalyzed reaction of allyl alcohol, 49, with methyl acrylate, 54, led to methyl sorbate, 55, albeit in low yield\textsuperscript{13} (scheme 12). And the reductive coupling of allyl alcohol with acetone, 4, gave alcohol 56 in 89% yield\textsuperscript{14} (scheme 13).

A more general study of allyl alcohol substitution initiated by palladium described by Atkins, et al.\textsuperscript{15}
Treatment of acetylacetone, 57, with allyl alcohol in the presence of Pd(acac)$_2$ furnished alkylation products 58 and 59. That a π-allyl intermediate was possibly involved, was indicated when either alcohol 60 or 61 led to the same product 62 when reacted with 57 and the palladium catalyst. Phenylacetonitrile, 63, also proved to be susceptible to the same process, as shown in its conversion to 64 (scheme 14).

While the above schemes for hydroxyl group replacement by carbon nucleophiles appeared to be of practical value in some cases, this process could be combined with the introduction of another structural feature to render the reaction of further synthetic interest. Thus it was shown in some cases above that the major products of substitution contained less substituted double bonds and more highly substituted allylic carbons than the isomeric minor products. This, however, did not appear to be a general and predictable property of most of these systems. If an allylic substitution scheme could be devised in which the major or only product contained the more highly substituted allylic carbon, such a process would be of great synthetic interest. This can be illustrated by the extreme case in which the desired product would contain a quaternary carbon, a structural feature which historically has been quite difficult to introduce into synthetic targets.

A process incorporating both a single-step hydroxyl replacement and the predominant formation of products
with more highly substituted allylic carbons as a general feature was reported by Felkin, et al.\textsuperscript{16} in 1968. Felkin found that allylic alcohols reacted with Grignard reagents in the presence of a catalytic amount of bis(triphenylphosphine)nickel dichloride, \textsuperscript{65}. In the case of the Grignard reagent containing a relatively labile $\beta$ hydrogen, i.e. n-propylmagnesium bromide, hydrogenolysis of the alcohol largely occurred resulting in formation of both alcohol-derived and Grignard-derived olefins.\textsuperscript{16a,b} However, when the Grignard reagent contained no labile $\beta$ hydrogen, i.e. methylmagnesium or phenylmagnesium bromide, substitution took place\textsuperscript{16c,d} (scheme 15).

\textbf{Scheme 15}

In a systematic study of the reaction of the Grignard reagent without labile $\beta$ hydrogen,\textsuperscript{16d} Felkin investigated the effects of alcohol and ligand structure as well as demonstrated the likelihood of a $\pi$-allyl intermediate intervening in the reaction. Based on these studies, a catalytic cycle was proposed which contained a general mechanism rationalizing the results of the above studies.
The addition of three to four moles of methylmagnesium bromide to 0.1 mole \( \text{65} \) suspended in ether, followed by the addition of one mole of allyl alcohol, \( \text{49} \), led in one hour to \( \text{1-butene, 66} \), in 91% yield. Under similar conditions, phenylmagnesium bromide and \( \text{49} \) afforded allylbenzene, \( \text{57} \), while reaction of the same alcohol with benzylmagnesium bromide yielded \( 4\text{-phenyl-1-butene, 68} \) (scheme 16). It is important to note that Felkin observed no double bond migration or isomerization under the reaction conditions.

**Scheme 16**

\[
\begin{align*}
\text{49} \quad \text{RMgBr} \quad \text{65} \\
\begin{array}{c}
\text{R} \\
\text{R} = \text{Me} \\
\text{R} = \text{Ph} \\
\text{R} = \text{PhCH}_2
\end{array}
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>91</td>
</tr>
<tr>
<td>Ph</td>
<td>80</td>
</tr>
<tr>
<td>PhCH₂</td>
<td>90</td>
</tr>
</tbody>
</table>

In examining monosubstituted allyl alcohols, Felkin observed that \( \text{26, 29} \), and \( \alpha \text{-methylallyl alcohol, 22} \), each reacted with methylmagnesium and phenylmagnesium bromides in the presence of \( \text{65} \) to give mixtures of olefins (scheme 17). Each isomeric olefin gave rise to a unique product distribution. It could be seen from the data that with a single substitution on the terminus of the allyl system, a distinct preference for the formation of products containing a terminal double bond was in operation. This
may be contrasted with the formation of 24 (scheme 5) and 27, 28, and 30 (scheme 6).

Scheme 17

<table>
<thead>
<tr>
<th></th>
<th>R= Me:</th>
<th>R= Ph:</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>54.0</td>
<td>65.5</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>46.0</td>
<td>34.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;73</td>
</tr>
<tr>
<td>29</td>
<td>R= Me:</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90.2</td>
</tr>
<tr>
<td></td>
<td>R= Ph:</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;64</td>
</tr>
<tr>
<td>22</td>
<td>R= Me:</td>
<td>29.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>68.8</td>
</tr>
<tr>
<td></td>
<td>R= Ph:</td>
<td>39.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31</td>
</tr>
</tbody>
</table>

As a side process in the reaction of alcohol 22 with phenylmagnesium bromide in the presence of 65, Felkin observed that alcohol 69 was formed. This was rationalized through an addition to the double bond of the allylic alcohol followed by a $\beta$ hydrogen elimination yielding the side product 69 (scheme 18).

Scheme 18

\[
22 \xrightarrow{\text{PhMgBr}} 65 \xrightarrow{\text{Ni}} \xrightarrow{\beta-H \text{ elimination}} 69
\]

In contrast to the above results, trans-cinnamyl, 19, cis-cinnamyl, 70 and $\alpha$-phenylallyl alcohols, 43, each reacted with methylmagnesium bromide in the presence of 65 to give trans-1-phenyl-1-butene, 71 (scheme 19). This
finding indicated that the phenyl situated on the allyl system served to negate the previously demonstrated tendency toward the formation of products with terminal double bonds. Instead there seemed to be a strong tendency in these cases to form products with the double bond in conjugation with the phenyl group. This should be compared to the formation of 41 and 42 (scheme 5) as well as 43 and 44 (scheme 8).

Disubstituted allylic alcohols entered into the same reaction as the above alcohols, although the reaction times were somewhat longer. With trans-3-hydroxy-1-phenyl-1-butene, 62, both methylmagnesium and phenylmagnesium bromides in the presence of catalytic 65 led to only the corresponding trans, conjugated olefins, 72, 73 (scheme 20). The preference for conjugation with an existing phenyl group was evident once again.

Operating on 1-vinyl-cyclohexanol, 74, Felkin observed that methylmagnesium bromide/65 treatment, this time in benzene as solvent, led in 64% yield to a mixture of the
two expected olefins, 75 and 76. However, once again a distinct preference for the product containing the terminal double bond appeared to be in effect. Starting with allylically isomeric alcohol, 77, virtually the same product distribution was obtained but in lower yield and with a much longer reaction time (Scheme 21). Use of benzene as solvent rather than ether improved the rate of reaction in the above systems. It is important to note that the above results
amounted to a facile synthesis of a quaternary carbon system.

Introducing another structural permutation in the disubstituted allylic alcohol series, Felkin found that treatment of alcohol 78 with methylmagnesium bromide in the presence of 65 gave once again only conjugated products 79 and 80 (scheme 22). Evidently the second olefinic

Scheme 22

\[
\begin{align*}
\text{MeMgBr} & \quad \text{65} \\
78 & \quad \rightarrow \\
79 & \quad + \\
80 & \quad 64\%
\end{align*}
\]

group served, as the phenyl group did previously, to direct formation of conjugated products rather than products containing terminal double bonds and more highly substituted allylic carbons. This particular system also had the possibility of substituting endocyclically as the alcohol was doubly allylic. Felkin observed no substitution within the ring. And the last disubstituted allylic alcohol, 1-cyclohexen-3-ol, 81, failed to react with Grignard reagents under conditions similar to the above.

Felkin examined briefly the effect of ligand structure on the reaction of 22 with methylmagnesium bromide. When bis(triethylphosphine)nickel dichloride, 82, was employed as catalyst, the reaction produced the same three
olefins as before but in a completely different ratio (scheme 23). Substitution of triethylphosphine for tri-

Scheme 23

\[
\begin{align*}
\text{MeMgBr} \quad \xrightarrow{\text{(Et}_3\text{P})_2\text{NiCl}_2} \quad & \quad \text{Me} \quad + \\
& \quad \text{Me} \quad + \\
\text{82} & \quad \text{83} \quad 55 : \leq 1 : 45 \quad \text{84} \quad \text{85}
\end{align*}
\]

phenylphosphine in the catalyst complex also decreased the rate of reaction considerably. Thus, Felkin reasoned that since the phosphine structure profoundly influenced the rate and product distribution of the above reaction, at least one phosphine must have remained coordinated to the nickel atom throughout the reaction. He speculated that perhaps both phosphines remained bound, however.

In fact, chelating diphosphine-containing catalysts, (1,2-(diphenylphosphino)ethane)nickel dichloride, 86, and (1,3-(diphenylphosphino)propane)nickel dichloride, 87, proved to be effective and their corresponding rates were similar to those of reactions carried out with bis(diphenylmethylphosphine)nickel dichloride, 88. Of course, dissociation of one phosphorus from nickel would be expected to be unfavorable for these chelating ligands.

From the above data it seemed obvious that the conversion of allyl alcohols to olefins could proceed through either a combination of SN2 and SN2' processes or alternatively through the intermediacy of \(\pi\)-allyl nickel
species. In support of the latter, Felkin noted that both 74 and 77 gave rise to the same product distribution when treated with methylmagnesium bromide and 65. This result was compatible with both alcohol isomers leading to the same \( \pi \)-allyl complex which was then converted to a mixture of products independent of the alcohol precursor (scheme 24). Furthermore, the fact that both alcohols gave

\[\text{Scheme 24}\]

the same product mixture did not seem to be consistent with an SN2/SN2\' type of mechanism.

To further support the \( \pi \)-allyl mechanism, Felkin established a stereochemical criterion for product formation from isomeric allyl alcohols. Considering the three isomeric butenols, 26, 29, and 22, if a \( \pi \)-allyl mechanism was operative, then this intermediate could exist in two possible stereochemical forms, a "syn" complex, 89, and "anti" complex, 90. At least initially, 26 would be expected to lead to the "syn" complex and similarly, 29 to the "anti" complex. However, 22 would be expected to
give a mixture of both \( \pi \)-allyl complexes, each of which would lead to product mixtures identical to those formed independently from their respective precursor alcohols, 26 and 29 (scheme 25). Thus upon conversion to the olefin mixture, 22 would provide 91, 92, and 93, the distribution of which would have to correspond to the weighted distribution of the same olefins derived from 26 and 29, respectively. The weighting factor would be the ratio \( k_s/k_a \), and demonstration that it was the same for each olefin for a particular Grignard reagent would constitute evidence that common intermediates were involved for the set of

Scheme 25

\[ \begin{align*}
26 & \quad \begin{array}{c}
\text{[Ni]} \\
\downarrow \quad k_s \\
\end{array} \\
\text{89} & \quad \text{ } \\
\text{91} & \quad \begin{array}{c}
\text{R} \\
\end{array} \\
22 & \quad \text{ } \\
29 & \quad \begin{array}{c} \\
\text{[Ni]} \\
\downarrow \quad k_a \\
\end{array} \\
\text{90} & \quad \text{ } \\
\text{92} & \quad \begin{array}{c}
\text{R} \\
\end{array} \\
\text{93} & \quad \begin{array}{c}
\text{R} \\
\end{array} \\
\end{align*} \]

\[ \frac{k_s}{k_a} \]

\[ \begin{align*}
R = \text{Me}: & \quad 0.90 \\
R = \text{Ph}: & \quad 1.3 \\
\end{align*} \]
three alcohols. Calculation of the weighting factor, $k_s/k_a$, could be made through

$$k_s/k_a = (X_{22}-X_{29})/(X_{26}-X_{22})$$

where $X_n$ stood for the percentage of olefin $X$ derived from alcohol $n$.

In fact, Felkin did observe identical $k_s/k_a$ values, within experimental error, for the cases of methylimagnesium and phenylmagnesium bromide treatment of alcohols 26, 29, and 22 in the presence of catalytic 65. Thus the $SN2/ SN2'$ combination of mechanisms seemed to be ruled out and the set of common $\pi$-allyl intermediates supported by these data. However, it was possible to gain further mechanistic insight into the reaction from the $k_s/k_a$ values. For example, Felkin observed that since the values for $k_s/k_a$ for both Grignard reagents were very close to unity, the rates of conversion of $\alpha$-methylallyl alcohol, 22, to $\pi$-allyl intermediates 89 and 90 were about equal. Furthermore, it was pointed out that the interconversion of $\pi$-allyl intermediates was slow relative to conversion to products: if it was fast then each alcohol would have given the same product distribution and if the interconversion did not occur at all the reaction would be stereospecific with 26 giving 91 and 92 and 29 giving 92 and 93. Felkin observed that the product distribution more closely resembled the latter situation.

At this point, Felkin suggested a catalytic cycle for the process of allyl alcohol substitution by Grignard reagents in the presence of nickel catalysts (scheme 26). The first step was the reduction of the bisphosphinenickel
dichloride complex, 94, which was brought about by alkylation by the Grignard reagent. The resulting species, 95, then expelled coupling product 96 to give 97. This process of expulsion of the coupled 96 was suggested to be acti-
vated by the presence of excess Grignard reagent. Felkin cited as evidence for this intermediacy of the bisphoshphinenickel complex 97 the fact that ethane was evolved upon reaction of 65 with methylmagnesium bromide. But in addition, this species could be generated independently from (Ph₃P)₄Ni, 104, and (Ph₃P)₂Ni(C₂H₄), 105, presumably through ligand dissociation. For example, treatment of 22 with methylmagnesium bromide in the presence of 104 led to an olefinic mixture quite similar to that produced from the same alcohol and Grignard reagent in the presence of 65. Alternatively, treatment of 26 with methylmagnesium bromide in the presence of 105 led to an olefin mixture also similar to that produced through the agency of 65 (Scheme 27).

```
Scheme 27

\[ \text{MeMgBr} \rightarrow \]

<table>
<thead>
<tr>
<th></th>
<th>83</th>
<th>84</th>
<th>85</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>104: 29</td>
<td>3</td>
<td>68</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>83</th>
<th>84</th>
<th>85</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>105: 52</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>
```

The second step was suggested by Felkin to be the oxidative addition of Grignard reagent across 97 to give an intermediate, 98, with a Ni-Mg bond, a structural feature which was also present in 99. To demonstrate that Ni-Mg bonded intermediates were present in the
catalytically active reaction mixture, Felkin treated 65 and 107, generated in situ, with methylmagnesium bromide and then carbon dioxide and obtained 106 and 108, respectively (scheme 28). Felkin also obtained evidence that

Scheme 28

\[
\begin{align*}
&65 \quad (\text{Ph}_3\text{P})_2\text{Ni(CO)}_2 \\
&1. \text{MeMgBr} \quad 106 \\
&2. \text{CO}_2 \\
&\text{[(C}_6\text{H}_5\text{)}_3\text{P}]_2\text{Ni} \\
&107 \\
&\text{[(C}_6\text{H}_5\text{)}_3\text{P}]_2\text{Ni(CO)}_2 \\
&108
\end{align*}
\]

other transition metal complexes which possessed metal–Mg bonds underwent similar carbonylation reactions by carbon dioxide. For example, treatment of complexes 109 and 110 with carbon dioxide gave corresponding carbonyl species (scheme 29). Felkin, et al.\textsuperscript{17} had gathered X-ray crystallographic data indicating that 109 definitely possessed an Fe–Mg bond, making the carbonylation of this substrate by CO\textsubscript{2} a plausible model for the similar reaction above carried out on the suspected Ni–Mg bonded systems. Thus Ni–Mg bonded intermediates were implicated in the allyl alcohol substitution scheme.

After the formation of a π-olefin complex, 99, with the magnesium alkoxide derived from the allylic alcohol substrate, the catalytic cycle continued through the rate determining step to form the π-allyl complex, 100. This
was shown to occur in all probability with inversion of configuration at the hydroxyl-bearing carbon.

Finally, Felkin suggested that in the collapse of the \( \pi \)-allyl complex to olefinic products, \( \text{102, 103} \), the product distribution, in the absence of an appending phenyl or olefinic group, was largely determined by the known preference for Ni to complex less substituted olefins, therefore explaining the tendency toward the formation of olefins with terminal double bonds.

Felkin, Wenkert, et al.\(^{18}\) determined the stereochemistry of the methylation of conformationally anchored the vinylcyclohexanol in the presence of \( \text{65} \), and applied these results to partial syntheses in the diterpene field. Starting with either of the two epimeric alcohols, \( \text{13 or 14} \), treatment with methylmagnesium bromide and catalytic \( \text{65} \) led to the same product distribution in which the product of equatorial
methyl introduction, 16, predominated (scheme 30). These results should be compared to the previously mentioned transformation of 13 and 14 into 15, 16, and 17 in which 15 was the major component (scheme 4). Observation of identical

Scheme 30

<table>
<thead>
<tr>
<th></th>
<th>15</th>
<th>16</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>20</td>
<td>76</td>
<td>4</td>
</tr>
<tr>
<td>MeMgBr</td>
<td>65</td>
<td>18</td>
<td>77</td>
</tr>
</tbody>
</table>

Product mixtures regardless of which allylic alcohol epimer 13 or 14 was used indicated that isomeric \( \tau \) -allyl moieties 111 and 112 were equilibrated readily. Furthermore, since equatorial methyl-containing product 16 was favored heavily, quasi-equatorial \( \tau \) -allyl 112 was preferred for steric reasons. Intermediate 112 would be expected to be the precursor of 16.

Observing that the steric situation and functionality presented by 16, i.e. axial vinyl, equatorial methyl groups attached to quaternized carbon, existed in the pimaradienic,
and 8-hydroxypimarene (exemplified by 114) diterpenes, Felkin and Wenkert applied the above results to a partial synthetic program in this area. Ketol 116, available in two steps from manool, 115, was treated with vinylmagnesium bromide to produce diol 117, which, in the presence of methylvinylmagnesium bromide and 65 afforded hydroxy olefin 118 (scheme 31). Addition of methyl to the primary ter-

Scheme 31
minus of the π-allyl was suggested to occur due to preferential interaction of Ni with both the alkoxide and the olefinic group of the product, a situation possible only if the double bond formed was the tri-substituted one.

Acid-catalyzed transformation of 116 into enone 119 was followed by addition of vinylmagnesium bromide to give the hydroxydienes mixture, 120, 121. Diene 122 resulted, when these hydroxydienes were subjected to methylmagnesium bromide / 65 treatment (scheme 32). This result was not surprising based on the previous report\textsuperscript{16d} of the conversion of 78 into 79 and 80 (scheme 22).

Thus while 8-hydroxypimarenic or \( \Delta^{8,14} \)-pimaradiene structures were not available by the above process, enone 119 could be used to produce a key intermediate en route to a more complex terpenoid system. Li/NH\textsubscript{3} reduction of
119 gave saturated ketone 123, which upon reaction with vinylmagnesium bromide led to a 1:1 mixture of allylic alcohols 124 and 125. The latter two substances in the presence of methylmagnesium bromide and 65 led to the mixture of olefins, 126, 127, and 128, with 126 predominating, as predicted by model systems 13 and 14. Utilization of 126 in a sequence leading to hibaene, 129, gave the natural product in five steps (scheme 33).

Scheme 33
Finally, de-conjugation of enone 119 followed by condensation with vinylmagnesium bromide led to the allylic alcohols 130 and 131 (ca. 1:1). These were treated with methylmagnesium bromide and 65 to produce 132 (scheme 34). Unfortunately, the final diene product is the only pimaradiene isomer 113 which has not yet been detected in nature.

Scheme 34

In undertaking a detailed study of the reaction of allyl alcohols with Grignard reagents which contained labile $\beta$ hydrogen in the presence of nickel catalysts, Felkin, et al. $^{16b}$ found that reaction of n-propylmagnesium bromide with 0.1 mol 65 led to the formation of propane and propene and upon addition of an allyl alcohol (1 mole), hydrogenolysis resulted. For example, 19 and 43 led to trans 1-phenyl-1-propene, 132, and allylbenzene, 67, in much the same ratios (scheme 35). Submission of 26, 29, and 22 to the same reaction conditions gave the butenes as shown (scheme 36). Propene was produced concurrently with the above olefin formation. In addition to the products mentioned, 43 and 22 also provided 1-phenyl-1-propanol, 136,
Felkin carried out the reaction of 22 with bis(tri-ethylphosphine)nickel dichloride, 82, and n-propylmagnesium bromide and obtained a butene mixture quite different from that with 65, showing again that the nature of the phos- phine could have a profound effect on the outcome of the reaction. However in contrast to this finding, 19 and n-propylmagnesium bromide in the presence of bis(diphenyl-
methylphosphine)nickel dichloride, 88, gave largely trans-1-phenyl-1-propene, 133, as with 65 (scheme 37).

Scheme 37

\[
\begin{array}{cccccc}
22 & 82: & 134 & + & 135 & + & 66 \\
\text{nPrMgBr} & \text{catalyst} & 14:36:50 & - \\
19 & 88: & 133 & + & 138 & + & 67 \\
90:2:8 & & & & & 76
\end{array}
\]

An important result also obtained with 88 was the reaction of 19 with n-propylmagnesium bromide in the presence of an excess of \((\text{Ph})_2\text{MeP}\) over that contained in the catalyst (scheme 38). The reaction was much slower than

Scheme 38

\[
\begin{array}{c}
19 \xrightarrow{\text{nPrMgBr}, 88} \text{catalyst} \rightarrow 133 + 67 + \text{Ph} \equiv \equiv \text{nPr} \\
90:10
\end{array}
\]

Alkylation/Reduction = \(A/R = 0.8\)

that carried out without excess phosphine but yielded a new product, trans-1-phenyl-1-hexene, 139. This reaction and others involving alkylation were performed by initial
set-up at liquid nitrogen temperature followed by warming to ambient temperature. In this way the ratios of alkylation to hydrogenolysis were reproducible.

Next, Felkin examined catalysts which contained chelating diphosphines such as 86 and 87. Exposure of the latter to \(n\)-propylmagnesium bromide and alcohols 19, 70, and 43 afforded both propylation and hydrogenolysis products, with the former predominating (scheme 39). A

**Scheme 39**

<table>
<thead>
<tr>
<th></th>
<th>133</th>
<th>138</th>
<th>67</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>A/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td></td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>76</td>
</tr>
<tr>
<td>70</td>
<td>(nPrMgBr)</td>
<td>87</td>
<td>72</td>
<td>16</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>43</td>
<td></td>
<td>82</td>
<td>7</td>
<td>12</td>
<td>9</td>
<td>57</td>
</tr>
</tbody>
</table>

similar reaction on alcohols 26, 29, and 22 also gave alkylation as well as reduction, but in this case the latter predominated (scheme 40). It was noted that while the alkylation product distribution was quite constant over both respective sets of alcohols, the hydrogenolysis mix-
Scheme 40

<table>
<thead>
<tr>
<th></th>
<th>134</th>
<th>135</th>
<th>66</th>
<th>134 + 135 + 66</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/R</td>
<td>73</td>
<td>3</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>69</td>
<td>3</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>52</td>
<td>8</td>
<td>26</td>
<td>50</td>
</tr>
</tbody>
</table>

nPr MgBr
tures were dependent on individual alcohol structure.

In comparison to the results with 87 and alcohols 19, 70, and 43, Felkin observed that 86 and n-propylmagnesium bromide reacting with the same alcohols gave less alkylation versus hydrogenolysis, although even with this catalyst, a preponderance of alkylation was observed (scheme 41).

Scheme 41

\[
\begin{array}{cccccc}
133 & 138 & 67 & \text{Yield (\%)} & \text{Yield (\%)} & \text{A/R} \\
133+138+67 & 139 & & & & \\
19 & 87.5 & 0 & 12.5 & 11.4 & 72.6 & 6.4 \\
70 \xrightarrow{nPrMgBr} 86 & 87.3 & 4.4 & 8.3 & 18.4 & 62.6 & 3.4 \\
43 & 93.1 & 0 & 6.9 & 30.2 & 60.3 & 2.0 \\
\end{array}
\]

Since the trend observed with 86 and 87 regarding alkylation versus reduction of allylic alcohols was 87 leading to more alkylation than 86, Felkin attempted to prepare the catalyst with the next higher chelating phosphine homologue, 142. However, only insoluble material, 

\[
\begin{align*}
\text{Ph}_2 \\
\text{(CH}_2)_4 \text{P} \\
\text{NiCl}_2 \\
\text{Ph}_2
\end{align*}
\]

which probably had polymeric structure 143, was obtained. Use of this material with n-propylmagnesium bromide and
either 19 or 43 led to alkylation/reduction ratios of only 0.1.

In explaining the results obtained with \( \text{n-propylmagnesium bromide} \), Felkin suggested that the mechanism of the process leading to the propylation products was exactly the same as that involved in the reactions utilizing Grignard reagents without \( \beta \) hydrogen.\(^{16d}\) However the mechanism of the process leading to the hydrogenolysis products was obviously quite different and Felkin modified his original scheme of allyl alcohol substitution to encompass these reactions.

As an explanation of the origin of the hydride involved in the hydrogenolysis step, Felkin proposed scheme 42. Noting that the Grignard reagent containing labile \( \beta \) hydrogen made a \( \beta \) elimination to give \(^{146}\) possible, Felkin proposed this fact as the cause for the introduction of hydride into the catalytic cycle\(^{16d}\) \(^{146}\) (scheme 26) as well as the formation of propene during the reaction. Such a scheme could explain also the effect of the phosphine on the alkylation/reduction ratio. Since the \( \beta \) elimination had been shown\(^{19}\) to require a prior ligand dissociation leading to \(^{146}\), for example, this would be retarded by excess phosphine (scheme 38) or chelating phosphines (schemes 39–41).
Furthermore, Felkin proposed that the alcohol structure would be expected to have an effect. This was due to the fact that \( \pi \)-allyl formation was supposedly rate determining and therefore a 144, 149 equilibrium would be established prior to this step. In so far as the alcohol structure would be expected to affect this equilibrium, those alcohols which favored 149 would lead to greater amounts of propylation whereas those that produced largely
would give greater amounts of hydrogenolysis. Thus, phenyl-containing alcohols 19, 20, and 43 led to greater amounts of propylation than 26, 29, or 22 and α-methyl-allyl alcohol, 22, led to more propylation than cis (29) and trans (25) crotyl alcohols. This was rationalized by noting that Ni-π-olefin complex stability is ordered as follows: Ph > 1-hexene > 2-hexene and therefore 19, 20, and 43 as well as 22 would favor 149 relative to 26 and 29 which would favor 144.

Employing the stereochemical criterion for π-allyl formation used before, \(^{16e}\) Felkin showed that for hydrogenolysis by \(n\)-propylmagnesium bromide \(k_s/k_a\) values for 26, 29, and 22 were 0.71, 0.44, and 0.54 respectively. These values were significantly different from each other and as these differences could not be ascribed to experimental error, Felkin concluded that the π-allyl mechanism was not the only one operative for the hydrogenolysis reactions and proposed another route (scheme 43).

**Scheme 43**

Felkin also pointed out that in the formation of 140 and 141 from 26, 29, and 22 with (1,3-(diphenylphosphino)-
propane)nickel dichloride, 87, the product distribution was independent of starting alcohol. This phenomenon was quite different than that observed with 65 as alcohols 26, 29, and 22 each gave unique product distributions with both phenylmagnesium and methylmagnesium bromides. Felkin suggested the explanation to lie in the rapid interconversion of the "syn", 150, and "anti", 151, \( \pi \)-allyl intermediates, indicating that each alcohol led to the same \( \pi \)-allyl isomer distribution, and therefore the same product distribution, with 87 as catalyst (scheme 44). This

Scheme 44

\[
\begin{align*}
\begin{array}{c}
\text{Ph}_2\text{P} \backslash \text{PPh}_2 \\
\text{Ni}-\text{nPr}
\end{array}
\rightleftharpoons \begin{array}{c}
\text{Ph}_2\text{P} \backslash \text{PPh}_2 \\
\text{Ni}-\text{nPr}
\end{array}
\end{align*}
\]

150 151

effect seemed to be a function of the chelating phosphine, since Felkin noted that Grignard reagents without \( \beta \) hydrogen in the presence of 86 produced the same lack of dependence of product distribution on alcohol isomer.

In contrast to nucleophilic replacement at an allylic site, substitution at an olefinic or aryl center has received much less attention. Recently olefinic and aryl halide replacement by Grignard reagents in the presence of nickel catalysts has been reported.20,21 These systems
were found to accept Grignard reagents with labile \( \beta \) hydrogen without effecting hydrogenolysis in most cases. When hydrogenolysis was a problem, chelating phosphine ligands retarded this process.

Kumada, et al.\(^{22}\) reported that chlorobenzene was substituted by ethylmagnesium bromide in the presence of catalytic \( 86 \) giving ethylbenzene in high yield (scheme 45). Using \( \text{Ni(acac)}_2 \) as catalyst, Corriu and Massé\(^{23}\)

**Scheme 45**

\[
\text{PhCl} \xrightarrow{86} \text{EtMgBr} \quad \xrightarrow{\text{PhEt}} \quad 98\%
\]

were able to effect arylation of bromostyrene with \( m \)-methylphenylmagnesium halide giving unsymmetrical \( \text{trans} \) stilbene, \( 152 \) (scheme 46).

**Scheme 46**

\[
\text{Ph} = \underset{\text{MgBr}}{\text{Br}} + \overset{\text{Ni(acac)}_2}{\text{O}} \xrightarrow{152} \text{Ph}
\]

Jolly and Wilke\(^{21}\) have reviewed the mechanism for these reactions which is depicted in scheme 47.

Reports have appeared concerning the replacement of olefinic and aryl sulfur functionality by organometallic reagents. Posner and Brunelle,\(^{24}\) for example,
found that olefinic sulfide 153 in the presence of lithio di-n-butylcuprate produced 1-phenyl-1-hexene, 154 (scheme 48). Okamura, Miura, and Takei25 showed that upon catal-

Scheme 48

sis by 65, Grignard reagents and olefinic sulfides combined to produce sulfur-replaced alkenes, as evidenced by the conversion of 155 to 156. This latter reaction also served to demonstrate the retention of sulfide configuration in the product olefin. These workers also observed the replacement of aryl sulfide functionality
in the conversion of 157 to 158 (scheme 49). Shortly after the report of the Japanese workers, Wenkert, et al., demonstrated once again the facility of nickel-catalyzed substitution of olefinic and aryl sulfur functionality by alkyl or aryl groups derived from Grignard reagents. For example, 1-methylthio-1-octene, 152, could be converted to 2-nonene, 160, and 1-phenyl-1-octene, 161, upon reaction with catalytic 65 and methylmagnesium and phenylmagnesium bromides, respectively. Retention of sulfide geometry in the products was obtained in both cases. Thioanisole, 157, could be converted to p-methylbiphenyl, 162, by reaction with p-tolylmagnesium bromide and catalytic 65, and indeed an extended series of examples of substitutions on aryl systems was reported. Although the thio compounds remained inert to treatment with ethylmagnesium bromide and 65, the same Grignard reagent and 86 acted on 163 to give ethylation product 164, unaccompanied by the expected reduction co-product, tert-butylbenzene (scheme 50). Wenkert, et al. found
that this novel carbon–carbon bond forming scheme was not confined to sulfide functionality but in fact could be extended to the replacement of mercaptide, sulfoxide, sulfone, sulfinate, and even selenide groups. Julia has also reported the nickel-catalyzed substitution of olefinic sulfone moieties by methylmagnesium halides. Another instance of aromatic sulfur replacement by carbon was provided by the reaction of 165 with styrene, 166, under palladium catalysis. Products 167 and 168 resulted, the latter becoming the major product when the olefin was deleted from the reaction mixture (scheme 51).

Although treatment of O-acetyl dimerone, 169, with
lithio dimethylcuprate afforded the β-methyl cyclohexenone, 170, in good yield\(^{29}\) (scheme 52), nucleophilic replacement of simple enol derivatives has undergone far less investigation than the cases cited above. One of

the earliest reports of such a process was that by Heck\(^{30}\) in 1968 who employed the palladium mediated arylation of enol esters and ethers by organomercury species. For example, phenylmercuric chloride, 171, and vinylacetate, 172, in the presence of catalytic Li\(_2\)PdCl\(_4\), 173, and cupric chloride as catalyst re-oxidant, led to stilbene, 174, and styrene, 166, products in which the acetoxy groups had been
replaced by phenyl. The products of phenyl introduction to the opposite end of the enol ether, 175 and 176 were also obtained. When an enol ether was employed, phenyl-mercuric chloride treatment in the presence of LiPdCl₃, 177, and cupric chloride again led to oxygen replacement by a carbon nucleophile (scheme 53).

Scheme 53

\[
\begin{align*}
\text{PhHgCl} + \overset{\text{CuCl₂}}{\overset{\text{171}}{\text{OAc}}} & \rightarrow \overset{\text{PhCHO}}{\overset{\text{175}}{\text{CHO}}} + \overset{\text{33\%}}{\overset{\text{3\%}}{\text{PhOAc}}} \\
\text{PhHgCl} + \overset{\text{CuCl₂}}{\overset{\text{171}}{\text{O₅Bu}}} & \rightarrow \overset{\text{174}}{\text{Cl₄}} + \overset{\text{11\%}}{\text{PhOAc}}
\end{align*}
\]

Expanding on Heck's results, Arai and Daves found that more complex systems were also susceptible to the same processes as above. Utilizing substituted dihydro-pyrans 178 and 182, treatment with organomercurial 179 in the presence of Li₂Pd(OAc)₂Cl₂, 180, gave products 181 and 183, respectively. Both substances were derived from enol ether oxygen replacement by the organic moiety de-
rived from 179 (scheme 54). It is interesting to note that the enol ether double bond stereochemistry was preserved in both of the substitution products 181, 183.

Making use of lithio diorganocuprates once again, Blaszczak, et al.\textsuperscript{32} reported the replacement of the enol phosphate functionality by alkyl groups leading to olefins (scheme 55). However, this system appeared to be limited to the use of lithio di-\textit{n}-butylcuprate as the corresponding methyl cuprate gave much diminished yields.

\textbf{Scheme 55}

Replacement of olefinic and aromatic oxygen function-
ality by hydrogen has been the object of synthetic interest and several successful systems have been developed. Both Fétizon, et al.33 and Ireland, et al.34 reported the reduction of enol phosphate esters by lithium in amine solvents in the presence of a proton source. Ireland, et al.34b for example, observed that treatment of 184 with lithium in the presence of tert-butyl alcohol gave 185 in 85% yield (scheme 56).

Scheme 56

![Reaction Scheme]

A more recent approach to the reductive removal of olefinic phosphate esters is that of Welch and Walters35 who reported that such substances were converted to the corresponding olefin upon treatment with titanium metal in tetrahydrofuran (scheme 57).

Much more attention has been paid to the reductive removal of aromatic oxygen. One of the earliest reports of such a process was due to Kenner and Murray36 who demonstrated that aryl tosylates upon treatment with Raney nickel afforded the corresponding deoxygenated systems. For example, reaction of the tosylate of methyl salicylate, 186, with Raney nickel furnished methyl benzoate,
187, in high yield (scheme 58). Several variation of this scheme followed in which aryl sulfonates were treated with hydrazine in the presence of Pd/Ca\((\text{CO}_3)\),\(^{37}\) hydrogen and Pd/charcoal\(^{38}\) and in one instance\(^{39}\) Raney nickel once again.

Scheme 58

Aryl ethers have found some use as leaving groups in the reductive removal of aromatic oxygen. In an early report\(^{40}\) on the subject, a phenoxy group was removed reductively from 188 by sodium in liquid ammonia to give 189 (scheme 59). A further example\(^{41}\) indicated that
benzene could be obtained in high yield by the Raney nickel treatment of diphenyl ether. Pirkle and Zabriskie developed a two-step reductive removal of 2,4-dinitrophenyl ethers in which the diaryl ether was first catalytically hydrogenated and next combined with sodium in liquid ammonia. Such a process is illustrated in the conversion of 190 to 191 (scheme 60). This last technique seemed to be limited to cases in which the 2,4-dinitrophenyl ether moiety was flanked by at least one methoxy or hydroxy group.

Phenyltetrazolyl ethers have been shown to be removed reductively from aromatic structures through catalytic
hydrogenation. Biphenyl, 192, resulted from such treatment of 192 (scheme 61). Catalytic hydrogenation once again proved to be effective for the hydrogen replacement of the isoureia structure of 194 (scheme 62). A simple aryl urethane was deoxygenated by hydrogen treatment in the presence of palladium on charcoal (scheme 63).
Aryl phosphates were readily deoxygenated in the presence of sodium liquid ammonia\(^{46}\) (scheme 64). A later more detailed study\(^{47}\) confirmed these results. A recent report\(^{48}\) has indicated that aryl phosphates are cleaved in high yield by titanium to give the corresponding aromatic hydrocarbon. The diethylphosphates of both 1- (195) and 2-naphthol (196) led to naphthalene, 197, for example (scheme 65).
Discussion

Although the Felkin reaction, -- "the replacement of the hydroxy group of allyl alcohols by hydrogen or an alkyl function in the reaction of Grignard reagents with such alcohols in the presence of phosphine-ligated nickel dichloride,"\textsuperscript{49} -- has been shown previously\textsuperscript{16} to be feasible, the generality of the process regarding structural perturbations of the allyl alcohol and Grignard reagent has not been proven yet. In general, before such a scheme could be put effectively to practical use, the limitations imposed by the structural variations of the reactants would have to be known. Thus, a study of the structural changes in the allyl alcohol and Grignard reagent that the Felkin reaction would tolerate was undertaken.

Starting with an examination of the effect of hybridization changes at the magnesium-bearing carbon of the Grignard reagent, use was made of 1-vinylcyclohexanol,\textsuperscript{74}, as the standard allylic alcohol. This alcohol was chosen because products derived from it could possess either a quaternary carbon and a monosubstituted double bond or a tri-substituted double bond, -- that is, substitution could occur at either the tertiary or primary terminus of the allyl system. Thus, this alcohol would represent a simple system whose derived products would have the possibility of including a synthetically significant feature,-- the quaternized carbon.

Treatment of 65 (0.1 mole) with excess phenylmagnesium
bromide followed by introduction of alcohol 74 (1 mole) and overnight refluxing in benzene led in 55% yield to hydroxyl substitution products 198 and 199. The average ratio of 198 to 199 was 9.2:1, indicating that phenyl delivery to the tertiary terminus of the allyl system was a highly efficient process (scheme 66).

Scheme 66

\[
\begin{array}{cccc}
74 & \text{PhMgBr} & 65 & 198 \quad 199 \\
& & & 9.2:1 \quad 55%
\end{array}
\]

Since the sacrifice of more than an equivalent of the substituting Grignard reagent for the trivial purposes of alcohol deprotonation and catalyst complex reduction would be intolerable for most syntheses, investigation into the use of methylmagnesium halide, an expendable Grignard reagent, for these operations was initiated. Treatment of 65 and alcohol 74 with the stoichiometric amount of methylmagnesium iodide necessary for alkoxide formation and reduction of the catalyst, followed by introduction of phenylmagnesium bromide led in 56% yield to expected products 198 and 199. However, the ratio of tertiary to primary phenyl delivery had been reduced from 9.2:1 for the above case of catalyst reduction by phenylmagnesium bromide, to 2.9:1 when methylmagnesium iodide was involved as catalyst.
reductant (scheme 67). This clearly indicates a dependence of the nature of the catalyst on the Grignard reagent used to reduce it and suggests that the R- [Ni] species, where R is derived from the Grignard reagent, RMgX, employed in the reduction of complex 65, might persist throughout the catalytic cycle suggested by Felkin, et al.\textsuperscript{16d,e} (scheme 26).

In contrast to the success encountered with phenylmagnesium bromide, the reaction of vinylmagnesium bromide with 74 in the presence of 65 reduced by either vinylmagnesium bromide or methylmagnesium iodide did not lead to vinyl-transfer products 200 or 201 but to products of apparent hydrogen transfer 202, 203, and 204 (scheme 68).

Examining the use of halomagnesium acetylides in the allyl alcohol substitution process and adopting methylmagnesium halide reduction of complex 65 as a standard procedure, treatment of alcohol 74 with 1-hexynylmagnesium bromide in the presence of the same reduced catalyst 65
system (designated by \((\text{Ph}_3\text{P})_2\text{Ni}\)) led in 33% yield to tertiary substitution structure 205 as the sole isolated product. This result did not prove to be general for acetylenic Grignard reagents because application of trimethylsilylacetylenylmagnesium bromide, 206, in a reaction with alcohol 74 led not to the product of substitution at the tertiary terminus of the allyl structure, 208, but rather to structure 207 (scheme 69).

It might be suggested that the isomeric product, 208, although formed, could have been destroyed in an oligomerizing process involving nickel-catalyzed addition of Grignard reagent, 206, across the triple bond of 208 followed by further such additions. Such a reaction has
been reported\textsuperscript{50a} to occur in the presence of nickel catalysts and indeed a similar process\textsuperscript{50b-g} may well be responsible for the reduced yield associated with the formation of 205. In support of this suggestion, it was observed that in the conversion of 74 to 205, the use of excess magnesium acetylide led to much more complex mixtures over those reactions in which only the required amount was employed. This observation may indicate that the nickel-catalyzed addition of 1-hexynylmagnesium bromide across the product triple bond followed by further such additions in an oligomerizing fashion is a competing process accentuated
when excess Grignard reagent is employed.

Since the intermolecular introduction of a phenyl unit into the allyl system of 74 had given mainly the quaternary carbon-containing product 198, an intramolecular variation of this reaction was attempted next. Alkylation51 of imine 209 through sequential treatment with methylmagnesium iodide and dibromide 210, followed by hydrolytic work-up, led to bromophenyl ketone 211 in good yield. Treatment of this material with vinylmagnesium bromide furnished trans addition product 212 containing probably less than 5% of the corresponding cis isomer. However, operating directly on bromophenyl ketone 211 through addition of vinylmagnesium bromide followed by introduction of magnesium metal to form Grignard reagent 215 and finally addition of reduced 65 ((Ph3P)2Ni), afforded a mixture of tricycles 213, 214 in 19% yield (scheme 70).

As trans Grignard reagent 215 led in a non-specific fashion to tricycles 213, 214 in a 1:1 ratio, it seems obvious that, similar to the earlier observation of Felkin, Wenkert, et al.,18 α -alkyls 216 and 217 are readily equilibrated (scheme 71). Surprisingly, the overall rate of arylation for the intramolecular reaction was much less than that observed when phenyl was introduced intermolecularly. This may be a consequence of unfavorable geometric factors involved in intermediates 216 and 217 being reflected in the transition state(s) leading to their formation in the rate-determining step.

The production of tricycles 213 and 214 in 19% yield
was accompanied by a complex mixture of side-products, two of which proved to be \textit{218} and \textit{219}. The production of \textit{218}
can be compared with the product of related structure obtained in the reaction of 74 with vinylmagnesium bromide in the presence of reduced 65 (scheme 68). The origin of the methyl group in 219 most likely reflects the use of methylmagnesium iodide to reduce catalyst complex 65.

As part of the investigation of various structural types of Grignard reagents the indolylmagnesium halides were applied to the Felkin reaction. Besides the possible contribution to basic indole chemistry nickel-catalyzed allyl alcohol alkylation of these special Grignard reagents, in principle, could yield efficient entries into such natural systems as that represented by the mold metabolite echinuline, \(^{52}\) 220. In particular, the dimethylallyl unit located at C2 of the indole nucleus could be envisioned to be particularly amenable to introduction through the
Felkin reaction applied to a suitably constructed indolyl-
magnesium halide and dimethylallyl alcohol.

Treatment of indole, allyl alcohol, and complex 65
with the stoichiometric amount of methylmagnesium iodide
required for indole and alcohol deprotonation as well as
complex 65 reduction led in 59% yield to 3-allylindole
221 with none of the corresponding 1-allylindole, 222,
being detected (scheme 72).

Scheme 72

Considering that 222 was perhaps the kinetic product
of the allylation, which, under the reaction conditions,
was rearranged rapidly to the observed product, 221, com-
 pound 222 was subjected to the conditions of the reaction
(i.e. treatment with 0.1 equivalent reduced complex 65)
and surprisingly no 3-allylindole, 221, was detected.
Instead, 222, was recovered along with an approximately 10% yield of indole (scheme 73). When a similar reaction was carried out in the presence of excess methylmagnesium iodide and complex 65, complete de-allylation resulted in a 94% yield of indole, a reaction which did not occur in the absence of 65. If phenylmagnesium bromide was used in the place of methylmagnesium iodide and in the presence of reduced 65, 222 afforded indole again but in this case allylbenzene, 67, was detected as well (scheme 74). These
results seem to indicate the indole moiety is merely functioning as the hydroxyl in the allyl alcohols, that is, as a leaving group for π-allyl formation in a normal Felkin catalytic scheme. This is particularly evident in the transfer of allyl from 222 to phenylmagnesium bromide in the presence of reduced 65. Nitrogen de-allylation by nickel catalysts have been observed previously.53

As the efficacy of indolylmagnesium halide in the Felkin reaction with allyl alcohol had been demonstrated, the use of the structurally more interesting dimethylallyl alcohol was investigated next. Reaction, as above, of indolylmagnesium iodide with dimethylallyloxide 224 in the presence of reduced 65 led in 29% yield to a 3:1:1 mixture of 225 and 226 (scheme 75). Again, no N-substitution was observed. It may be noted that reproducibility of this particular process was obtained only when the technique of freezing the reactants with liquid nitrogen followed by slow warm-up to ambient temperature16b was
employed. Of course, the successful use of dimethylallyl alcohol in such an alkylation of indole not only boded well for application to the synthesis of echinuline-type natural products, but more fundamentally represented a useful construction of quaternized carbon units directly attached to indole.

Although alkylation of indole with dimethylallyl alcohol had been moderately successful, the test of such a process regarding possible utility in construction of the mold metabolites illustrated by echinuline, 220, would be the alkylation of an already 3-substituted indolylmagnesium halide. Operation on skatole-derived Grignard reagent 227 and treatment with allyloxide in the presence of reduced 65 led in 16% yield to indole 228, the product of substitution at C2 of the indole nucleus (scheme 76). Of course, the allyl unit of greatest interest would be that introduced by alkoxide 224. However, treatment of indolylmagnesium iodide 227 with 224 in the presence of reduced 65 did not afford either of the isomeric products 229 or 230, skatole being the only recovered material. This
last failure and, indeed, the generally low yields associated with the indole reactions can be attributed to low rates of reaction encountered whenever the indole or allyl alcohol components were moderately substituted, resulting in the diversion of starting material into side processes. Employment of a higher boiling solvent, such as toluene, did not enhance product formation, but, instead, produced decomposition of the catalyst.

At this point it was decided to leave the problem of the variation of Grignard reagent structure and focus on structural perturbations of the allyl alcohol component. Although Felkin, et al. had previously attempted substitution of cyclohexenol, $^{16d}$ 81, a further attempt seemed justified. This particular allyl alcohol was of interest, because the intermediate $\pi$-allyl, $^{231}$, would be constrained in a completely anti stereochemical form, a $\pi$-allyl structural feature known to be unfavorable relative to the two other possibilities, $^{232}$ and $^{233}$, at least where $M=Fe$. $^{54}$ In fact, treatment of 81 with phenylmagnesium bromide in the presence of reduced $^{65}$ led smoothly to phenylcyclohexene $^{234}$ in 69% yield (scheme 77).

Next it was desired to test whether the $\pi$-allyl system could tolerate not only being placed within a six-
membered ring but having affixed to it a high degree of substitution as well. Starting with 3-methylcyclohexenone, 235, addition of methylmagnesium bromide gave allyloxide 236 which, in the presence of phenylmagnesium bromide and reduced 65 gave not only 237, the expected product, in 7% yield but also a 21% yield of dimer 238 as a mixture of diastereomers. Likewise, utilization of methylmagnesium bromide throughout and in the presence of 65 led to none of the hoped-for 1,3,3-trimethylcyclohexene, but instead gave the same allyl dimer 238, this time in 27% yield (scheme 78). Clearly, the above system was involved in processes quite different than those encountered in the normal Felkin reaction.

In view of the peculiar hydrogen transfer products encountered in the attempted vinylation of 74 (scheme 68)
it was thought that perhaps this process could be related to that illustrated by the formation of 238 (scheme 78). The disproportionation reaction was not one that had only shown itself in the reaction of vinylmagnesium bromide with 74 in the presence of 65, but indeed a disproportionation product had been detected by Felkin, Wenkert, et al. in the reaction of 13, 14 epimers with methylmagnesium bromide in the presence of 65 (scheme 79). A related product, 218, had been observed as well from the reaction of 215 with reduced 65 (scheme 80). And upon careful examination of several reactions of alcohol 74.
with Grignard reagents such as phenylmagnesium bromide and 1-hexynylmagnesium bromide in the presence of reduced 65, conditions that led to normal Felkin reaction products, compounds 202, 203, and 204 could be detected also, albeit in trace quantities (scheme 81). Thus it appeared that the disproportionation or hydrogen transfer process was perhaps a general phenomenon which became a major reaction when something interfered with the Felkin catalytic cycle (scheme 26).

It was decided to investigate the disproportionation reaction given by 74 and vinylmagnesium bromide in the
presence of 65 through labeling experiments employing tetradeutero alcohol 239. Subjection of this alcohol to

the reaction with vinylmagnesium bromide in the presence of reduced 65 might be expected to lead to hydrocarbons 240–242 if the origin of the hydrogen introduced in the mono-olefinic products is the group of hydrogens flanking the incipient \( \pi \)-allyl carbons. In fact, when alcohol 239 was treated with vinylmagnesium bromide in the presence of 65 and the reaction quenched with \( \text{H}_2\text{O} \), olefins 240 and 241 were detected, but instead of 242, the ethylidene product contained only protium in the methyl group, 243 (scheme 82). When, however, quenching was performed with \( \text{D}_2\text{O} \), incorporation of one D into the methyl group was observed, 244.

It seems possible that the disproportionation process just described could have one feature in common with the formation of dimer 238 at the point in the Felkin catalytic cycle at which these abnormal processes diverge from the usually encountered scheme. Since 202, 203, and 204 as well as 238 appear to be derived from \( \pi \)-allyl moieties, the Felkin mechanism may be followed up to and including the formation of intermediate 100, at which
point transfer of the R group to the σ-allyl structure becomes impossible due to structural or electronic features associated with either R or the π-allyl system itself.

As illustrated in scheme 83, intermediate 100 has at least one pathway for further reaction other than that associated with the normal Felkin scheme. The scheme illustrates a possible path to bis-π-allyl complex 245 involving in the crucial formation of the second π-allyl a process analogous to that which Felkin, et al., proposed for π-allyl formation.
Scheme 83

\[
\begin{align*}
&\text{RMgX} \rightarrow R-R \\
&\text{MgX} \rightarrow \text{MgO, MgX, 2L} \\
&\text{Ni} \rightarrow 2L, \text{NiL}_2 \\
&\text{Dimer} \rightarrow 2L, \text{NiL}_2 \\
&\text{MgX} \rightarrow \text{quench} \\
&\text{NiL}_2 \rightarrow \text{largely} \\
&\text{NiL}_2 \rightarrow \text{largely}
\end{align*}
\]
in the normal catalytic cycle. This species may be used to explain the phenomena associated with both the disproportionation reaction and dimer formation. For example, direct combination of the π-allyl units of 245 to give allyl dimer could explain the observations made on 236 in its reaction with methylmagnesium and phenylmagnesium bromides in the presence of reduced 65 to give 238. Such an intermediate has been suggested for the Ni(CO)₄-initiated coupling of allyl halides to give allyl dimers.⁵⁵

Alternatively, 245 could start the disproportionation process by transferring a hydrogen from one π-allyl moiety to nickel to give 246 and diene. This reaction could be operating through normal β hydrogen elimination in a σ-allyl structure illustrated in 247. Once hydro-

![Diagram](image)

247

gen has been transferred to nickel, further transfer to the remaining π-allyl might be expected to occur largely to the tertiary terminus of the allyl system, in analogy with the experience of the transfer of alkyl and aryl groups. Hydrogen transfer to give disproportionation products has been observed in a palladium π-allyl complex⁵⁶ and in nickel complexes as well.⁵⁵ Thus, products 202 and 203 have been rationalized.
For the explanation of the formation of 204 it must be remembered that one methyl hydrogen is derived from water used in the quenching step. Thus it might be proposed that 245 undergoes a transmetalation to give an allylic Grignard reagent. Such a process may be envisioned as merely the reverse of nickel bis-π-allyl formation in the reaction of an allylic Grignard reagent with an anhydrous nickel dihalide.\textsuperscript{57} Next, upon quenching, this species might be expected to acquire a proton largely at the primary terminus, thus explaining the incorporation of water hydrogen into the methyl group of 204.

A simple test of the above scheme for the formation of disproportionation products 202, 203, and 204 would be the independent generation of supposed intermediate 248 and subjection of it to conditions similar to those

\[
\begin{array}{c}
\text{Ni} \\
\text{248}
\end{array}
\]

in which 202, 203, and 204 were formed from alcohol 74. Unfortunately treatment of Grignard reagent 249 with anhydrous NiBr\textsubscript{2} under standard conditions for bis-π-allyl nickel formation\textsuperscript{57} did not lead to 248, thus thwarting attempts to verify the postulated mechanism (scheme 84). Quenching of 249 with water, however, indicated 204 to
be produced in excess over 203.

It is important at this stage to address the problem of why R in 100 is not transferred to the \( \pi \)-allyl unit to give normal substitution products. In the case of alkoxide 236 it is obvious that the nature of the \( \pi \)-allyl moiety determines the fate of intermediate 100, as both methylmagnesium and phenylmagnesium bromides behave normally with other allyl alcohol systems. The reason for the misbehavior of alkoxide 236 is certainly not apparent and further speculation is not possible. However in the case of the reaction of alcohol 74 with vinylmagnesium bromide in the presence of 65, the absence of R transfer may be attributed to the nature of this group, vinyl, attached to nickel, since alcohol 74 yields normal Felkin reaction products with other Grignard reagents. It is attractive to suggest that the reason for the vinyl group preferring to remain attached to nickel rather than suffering transfer to the \( \pi \)-allyl moiety is the substantial \( \pi \) interaction between the vinyl \( \pi \) bond and the metal in addition to a \( \sigma \) bond. Such a proposal would predict difficult vinyl transfers from nickel in
other contexts and indeed this has been found to be the case.\textsuperscript{58} It should be pointed out, however, that x-ray photoelectron spectral data have suggested that in some olefinic nickel $\sigma$ bonded species $\pi$ interactions are unimportant.\textsuperscript{59} Returning to the examination of different allyl alcohols in the Felkin reaction, one structural feature which Felkin had not examined was substitution on the central carbon of the allyl system. Operating on isopropenylcyclohexanol, \textsuperscript{250}, treatment with phenylmagnesium bromide in the presence of reduced \textsuperscript{65} led in 63\% yield to a single product, \textsuperscript{251}. Alternatively, reaction of alcohol \textsuperscript{250} with methylmagnesium bromide in the presence of \textsuperscript{65} did not afford the expected products \textsuperscript{252} or \textsuperscript{253}, starting alcohol \textsuperscript{250} being recovered in this case (scheme 85).

\textbf{Scheme 85}

\begin{center}
\begin{tikzpicture}
  \begin{scope}
    \node at (0,0) {\textbf{250}}; \node at (1.5,0) {PhMgBr}; \node at (3,0) {Ph}; \node at (0,-1.5) {OH}; \node at (1.5,-1.5) {\textbf{63\%}}; \node at (3,-1.5) {\textbf{251}};
  \end{scope}
  \begin{scope}[shift={(-4,0)}]
    \node at (0,0) {\textbf{252}}; \node at (1.5,0) {Me}; \node at (0,-1.5) {\textbf{250}};
  \end{scope}
  \begin{scope}[shift={(-4,-3)}]
    \node at (0,0) {\textbf{253}}; \node at (1.5,0) {Me}; \node at (0,-1.5) {\textbf{250}};
  \end{scope}
\end{tikzpicture}
\end{center}
The use of functionalized allyl alcohols in the Felkin scheme would be expected to extend the synthetic utility of such a process. One such example of further functionality which could be introduced directly on the allyl system was the alkoxy group, as in methoxyalcohol 254. Products derived from such a substrate would of course be expected to possess enol ether groups whose hydrolysis would furnish ketones, a useful modification of Felkin's original allyl alcohol substitution process. It was therefore surprising to find that subjection of alcohol 254 to the conditions of excess phenylmagnesium bromide treatment in the presence of reduced 65 led not only to replacement of the hydroxyl by phenyl but to replacement of the olefinic methoxy group as well, giving hydrocarbon 255 in 46% yield. When one equivalent of phenylmagnesium bromide was employed in the reaction, a ca. 1:1 mixture of alcohol 254 and 255 was obtained, indicating that the second substitution step is faster than the first. Likewise, reaction of 254 with methylmagnesium bromide in the presence of 65 yielded not a methylated enol ether system but rather alcohol 250, the product of substitution of the methoxy group only (scheme 86).

There are two possible mechanistic explanations for
Scheme 86

\[
\begin{align*}
\text{excess} & \quad \text{PhMgBr} \quad 255 \\
254 + (\text{Ph}_3\text{P})_2\text{Ni} & \quad \text{1 equiv.} \quad \text{PhMgBr} \quad 254 + 255 \\
& \quad \text{MeMgBr} \\
& \quad 250 \quad 72\%
\end{align*}
\]

these results. First of all, it appears that the methoxy substitution might be a non-nickel catalyzed event as Felkin, et al.\textsuperscript{60} have previously shown that allyl alcohols are subject to Grignard reagent addition across the double bond with the alkyl moiety of the Grignard reagent becoming attached to the central carbon of the allyl system. Invoking such a reaction on a 2-alkoxy allyl alcohol, 256, would lead to 257 which now has a leaving group \( \beta \) to the magnesium and so would be expected to give 258. Of course, 258 could now suffer the normal Felkin reaction. An alternative scheme would be the addition of a R-Ni species across the double bond of 256 to give 259 which then might undergo transmetalation 257, or eliminate the RO- unit to give directly 258 (scheme 87). The addition of Grignard-derived R-Ni species across double bonds has been noted
before.\textsuperscript{16d,61} Felkin, \textit{et al.}\textsuperscript{60} had suggested that the un-
catalyzed addition of Grignard reagents across allyloxy
double bonds was strongly dependent on the alkoxide directed
Mg-olefin interaction. It is not immediately clear whether
or not the nickel-mediated route would be similarly hy-
droxy1-dependent, but, since simple enol ethers without
nearby hydroxyl groups might be expected to be stable to
Grignard reagents alone, a test to detect the nickel-
catalyzed route to the enol ether substitution products
could be carried out by reacting enol ethers without neigh-
boring hydroxy groups in the presence of Grignard reagents
and reduced \textsuperscript{65}.

Exposure of methoxycyclohexene \textsuperscript{260} to phenylmagnesium
bromide in the presence of reduced \textsuperscript{65} under conditions
identical with those employed in the reaction on allyl
alcohols, led to \textsuperscript{261} in 71\% yield. Similar treatment of
\textsuperscript{262} led to \textsuperscript{263} in 75\% yield while reaction with methyl-
magnesium bromide in the presence of reduced 65 gave the corresponding methylated olefin 264 in 59% yield. Phenyl cyclohexene 261 resulted from the reaction of trimethyl-silyloxy-cyclohexene 265 with phenylmagnesium bromide and reduced 65 (scheme 88). Thus it appeared that the nickel-catalyzed enol ether substitution reaction occurred readily in the absence of a proximal hydroxyl group.

A test of the steric bulk that the above process would tolerate in the vicinity of the enol ether moiety was attempted next. Methoxycyclohexene 266 failed to give 267 when treated with phenylmagnesium bromide and reduced 65,
thus revealing that steric congestion about the enol ether hindered the substitution process. Enamines, as nitrogen analogues of enol ethers, were tested as substrates and were found to be ineffective, as in the attempted conversion of 268 to 261. The utility of enolates in this oxygen replacement reaction was examined, but treatment of isobuteryl acetate, 269, with two equivalents of methylmagnesium bromide, followed by introduction of phenylmagnesium bromide and reduced 65, did not lead to the formation of 270 (Scheme 89). These unsuccessful reactions revealed

Scheme 89

![Diagram showing the reaction schemes](image)

some of the limitations placed on the enol ether substitution process.

Since cyclic substrates 260, 262, and 265 had been effective in the formation of olefins when treated with
Grignard reagents and reduced \( \text{65} \), it became of interest at this point to find out if acyclic enol ethers reacted under these conditions, and if so, what the associated stereochemistry of the reaction might be. Treatment of enol ether mixture \( \text{271, 272} \) with phenylmagnesium bromide and reduced \( \text{65} \) led to \( \text{273, 274} \) in 86% yield. The isomer ratios of the product mixture (\( \text{273, 274} \)) when compared to that of the enol ether mixture (\( \text{271, 272} \)) indicated on overall inversion of enol ether stereochemistry in the products. In contrast to these results, enol ethers \( \text{275, 276} \) seemed to produce \( \text{277 and 278} \) in a ratio indi-

\[
\text{Scheme 90}
\]

\[
\begin{align*}
&\text{R} = \text{Ph}: \\
&\text{Z: 273 1} \\
&E: 274 3.1 \\
\end{align*}
\]

\[
\begin{align*}
&R = \text{Me}: \\
&E: 279 1.4 \\
&Z: 280 1 \\
\end{align*}
\]
ative of a retention of stereochemistry. When methylmagnesium bromide was used as the Grignard reagent, 275, 276 afforded olefins 279, 280, again in a process involving retention of stereochemistry (scheme 90). On the basis of the observations of Felkin, et al., the conversion of 271, 272, into 273, 274 was not expected to be accompanied by double bond isomerization leading to an equilibrium mixture of tri-substituted double bond isomers whose ratio fortuitously reflected inversion of enol ether stereochemistry. This also was demonstrated by the conversion of the 273, 274 mixture (1:3.1) obtained in the substitution process to a new mixture (1:1.3) by equilibration in the presence of thiophenol and azo-bis-isobutyronitrile (AIBN) at elevated temperature (scheme 91).

Scheme 91

\[
\begin{array}{c}
\text{273} & 1 \\
\text{274} & 3:1 \\
\text{PhSH} \quad \text{AIBN} \quad \Delta \\
\end{array}
\]

\[
\begin{array}{c}
\text{273} & 1 \\
\text{274} & 13 \\
\end{array}
\]

Dihydropyran, 281, proved to be susceptible to oxygen displacement when reacted with phenylmagnesium and methylmagnesium bromides in the presence of reduced 65 and afforded 282 and 283, 284, respectively, in good yields (scheme 92). Once again, overall retention of enol ether stereochemistry in the products was the predominant result.

Presumably, the interaction of a Grignard reagent with labile \( \beta \) hydrogen and an enol ether in the presence of
reduced 65 could produce either alkyl substitution or hydrogen substitution of the enol ether structure in analogy to the results of Felkin, et al.\textsuperscript{16a,b} in the allyl alcohol substitution reactions. This, in fact, proved to be the case as reaction of dihydropyran, 281, with ethylmagnesium bromide in the presence of 65 led to both hydrogen transfer and ethyl transfer products, 285 and 286, respectively. As Felkin, et al.\textsuperscript{16a,b} had previously observed an increase in the ratio of alkylation \textit{versus} hydrogenolysis of allyl alcohols by labile β hydrogen-bearing Grignard reagents upon changing from 65 as catalyst to 86 or 87, it was thought that the employment of 87 in the reaction of dihydropyran, 281, with ethylmagnesium bromide might produce the same effect. Reaction of 281 with ethylmagnesium bromide in the presence of 87 led to an enhancement in the ratio of 286 to 285 over the case in which 65 was employed as catalyst (4.8:1 \textit{versus} 1.6:1, scheme 93). Thus, it was
shown that the enol ether substitution process could, as the Felkin reaction had been before,\textsuperscript{16a,b} be extended to Grignard reagents containing labile $\beta$ hydrogen if a catalyst complex containing a chelating biphosphine ligand (i.e. \textsuperscript{87}) was used. The ethylation product \textsuperscript{286} once again exhibited retention of \textsuperscript{281} double bond geometry.

In view of the success in the oxygen replacement of enol ethers an attempt was made to extend this reaction to the use of aromatic ethers as substrates. Treatment of 2-methoxynaphthalene, \textsuperscript{287}, with phenylmagnesium bromide in the presence of reduced \textsuperscript{65} led to 2-phenynaphthalene, \textsuperscript{288}, in 76\% yield. Similar treatment of \textsuperscript{287} with methylmagnesium bromide, however, failed to generate 2-methynaphthalene. Reaction of 2-naphthol, \textsuperscript{289}, with phenylmagnesium bromide and reduced \textsuperscript{65} again afforded \textsuperscript{288} (scheme \textsuperscript{94}). Of course, this last reaction involved magnesium oxide as the formal leaving group and in this respect is similar to the Felkin reaction.

In considering possible mechanistic schemes to explain
the results obtained in the reactions of enol and aryl ethers with Grignard reagents in the presence of reduced 65, it is attractive to retain as much of the Felkin catalytic scheme (scheme 26) as possible. Thus it is almost certain that 97 is once again the true catalytic species which, after oxidative addition of RMgX affords 98. Coordination to the enol or aryl ether π system yields 289, analogously to 99 (scheme 26), which might be considered to have resonance structure 289b as a major canonical contributor. This last feature must be invoked to explain the efficacy of rather highly substituted enol ethers in the oxygen replacement reaction. Nickel-catalyzed Grignard reagent addition to olefins has in the past been efficient only for ethylene and monosubstituted cases.61 Thus there would seem to be a substantial electrophilic component to the reaction (scheme 95).

The next step in the proposed catalytic cycle for enol ether substitution is the transfer of R from nickel
to the oxygen-bearing carbon, producing 290. The latter then undergoes elimination of R'OMgX to furnish the nickel-complexed product 291, analogous to 101 (scheme 26). Upon interaction with more Grignard reagent the substitution
product 292 is released and 98 is regenerated, thus completing the catalytic cycle (scheme 95).

Of course, when a Grignard reagent with labile $^\beta$ hydrogen is employed, $R$ may in fact be H in scheme 95. Here again the electrophilic interaction suggested by 289b should be important since nickel-catalyzed hydride addition to double bonds only occurs with ethylene and mono-substituted olefins.\textsuperscript{61,63}

Incorporation of the predominant stereochemical result, retention of enol ether stereochemistry, allows two combinations of modes of addition / elimination for the substitution process. Thus, a \textit{cis} addition of $R$-Ni followed by a \textit{trans} elimination of $R'O$- M or a \textit{trans} addition, \textit{cis} elimination sequence would lead to retained stereochemistry in the product. As depicted in the proposed catalytic cycle (scheme 95), the conversion of 289 to 290 suggests a \textit{cis} addition which necessarily would be followed by a \textit{trans} elimination of alkoxide. The \textit{cis} addition of organonickel species to multiply bonded systems has been observed\textsuperscript{50} before, as has the \textit{cis} addition of an organopalladium complex to an olefin.\textsuperscript{64} It is not clear which of the two steps experiences a reversal of stereochemistry in the abnormal conversion of 271, 272, into 273, 274, a process apparently involving inversion of enol ether stereochemistry in the products.
Experimental

All reactions involving organometallic reagents were performed under argon using solvents which were either distilled from drying agents under argon immediately before use or were distilled and then stored under rigorously dry conditions. A typical work-up of nickel-catalyzed reactions is illustrated in the first experiments and thereafter indicated only by parenthetical listing of extraction solvent and drying agent.

Analytical gas chromatography was performed on a Varian 1200 (flame ionization) instrument employing 1 m x 0.125 in. columns of OV 101 (loading indicated) on Chromosorb W (80–100 mesh) while preparative gas chromatography was performed on an Aerograph Autoprep A-700 (thermal conductivity) instrument employing 10 ft. x 0.25 in. columns of OV 101 (loading indicated) on Chromosorb W (60–80 mesh). Infrared spectra were recorded on Perkin-Elmer 137, Beckman Acculab Model 8, and I.R. 8 spectrophotometers as neat thin films and are tabulated in cm⁻¹. ¹H NMR spectra were recorded on Varian A-56/60 (60 MHz), EM-390 (90 MHz), and XL-100-15 (100 MHz) spectrometers as carbon tetrachloride solutions with TMS as internal standard (δ = 0 ppm), unless otherwise noted. ¹³C NMR spectra were recorded on the Varian XL-100-15 instrument, operating at 25.02 MHz in the Fourier transform mode, as CDCl₃ solutions. Carbon shifts are reported in ppm downfield of TMS; δ (TMS) = δ (CDCl₃) + 76.9 ppm. Low resolu-
tion mass spectra were recorded at 70 eV on a Finnigan 3300 GC-MS spectrometer and ions with m/e > 40 and intensity > 20% of the base peak are listed. High resolution mass measurements were performed on either C.E.C. 21-11013 or Du Pont 21-110C instruments employing the peak matching method. Ultraviolet spectra were recorded on a Cary-17 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Inc.

1-Cyclohexylidene-2-phenylethane (199)

To 7.565 g (20.5 mmol) of triphenylvinylphosphonium bromide in 120 mL of dry ether was added 11.8 mL (20 mmol) of phenyllithium solution (1.7 M in benzene/ether, 70:30). After stirring at room temperature for 9 h, 3.920 g (40 mmol) of cyclohexanone in 20 mL of ether was added and the resulting mixture was refluxed for 11 h. At this point, the mixture was filtered through Celite and evaporated. The residue was placed on a silica column and eluted with petroleum ether, yielding an oil. Further purification by preparative TLC (silica) and elution with petroleum ether (3x) gave 251 mg (7%) of 199 as an oil which could be distilled evaporatively at 70-170°C (7 Torr): IR: 1670(w, C=C), 1605(m), 1495(s), 1455(s, aromatic C=C), 740(s), 700(s, mono-substituted aromatic); 1H NMR: δ 1.50-1.90(br s, 6, non-allylic CH2), 1.98-2.48(br s, 4, allylic CH2), 3.43(d, 2, J=8 Hz, allylic benzylic CH2), 5.22-5.58 (br t, 1, J=8 Hz, olefinic CH), 7.35(s, 5, aromatic H);
$^13$C NMR: 26.8, 27.8, 28.5, 28.7, 33.3, 37.1(CH$_2$), 119.5, 125.4, 128.0(multiple peak)(CH), 140.2, 141.7(quinatnaries); MS: 196(M$^+$,16), 104(100), 91(30); m/e (calcd. for C$_{14}$H$_{18}$, 186.1409) 186.1407. Anal. (calcd. for C$_{14}$H$_{18}$, C 90.26, H 9.74) C 90.20, H 9.64.

**Nickel Catalyzed Reaction of Phenylmagnesium Bromide with 74 (Catalyst Preparation with Phenylmagnesium Bromide)**

To 65 mg (0.099 mmol) of 65$^{67}$ in 2 mL of benzene was added 2.4 mL (2.4 mmol) of phenylmagnesium bromide solution (1 M in benzene) followed, after 0.25 h, by 137 mg (1.09 mmol) of 1-vinylcyclohexanol, 68 74, in 2 mL of benzene. The resulting mixture was refluxed for 13.5 h, cooled, quenched with saturated aqueous ammonium chloride, extracted with ether, dried (MgSO$_4$), and evaporated. Preparative TLC (silica) of the residue and elution with petroleum ether (2x) afforded 113 mg (56%) of a 13:1 mixture (GC, 2% OV 101) of 198 and 199, identical to an independently prepared sample (vide supra), as an oil. **198:** IR: 1630(m, C=C), 1600(m), 1495(s), 1450(s, aromatic C=C), 760(s), 700(s, monosubstituted aromatic); $^1$H NMR (CDCl$_3$): 8 1.0-2.26(m, 10, saturated CH$_2$), 4.68-5.08(m, 2, vinyl CH$_2$), 5.88(dd, 1, J=11, 18 Hz, vinyl CH), 6.96-7.76(m, 5, aromatic H); $^{13}$C NMR: 22.4, 26.3, 35.8(saturated CH$_2$), 44.6(saturated quaternary), 112.0(vinyl CH$_2$), 125.3, 126.5, 127.9(CH), 146.5(aromatic quaternary), 147.2(CH); MS: 186(M$^+$,17), 143(30), 130(28), 129(78), 128(55), 118(22), 117(39), 115(63), 105(34),
104(100), 95(24), 91(87), 77(30), 67(25), 65(22), 51(25), 41(37); m/e (calcd. for C_{14}H_{18}, 186.1409) 181.1406. Anal. (calcd. for C_{14}H_{18}, C 90.26, H 9.74) C 90.12, H 9.64.

Mixtures of 198, 199 could be separated by chromatography on 15% AgNO₃ on silica and elution with petroleum ether to give first 199 followed by 198.

Repetition of the above experiment led to an average yield of 55% and an average 198:199 ratio of 9.2:1.

**Nickel Catalyzed Reaction of Phenylmagnesium Bromide with 74 (Catalyst Preparation with Methylmagnesium Iodide)**

To 66 mg (0.1 mmol) of 65 in 2 mL of benzene was added 0.55 mL (1.27 mmol) of methylmagnesium iodide solution (2.3 M in ether) followed by 1 mL of benzene. After 10 min. 134 mg (1.06 mmol) of 74 in 2 mL of benzene was added and after gas evolution ceased, 1.06 mL (1.06 mmol) of phenylmagnesium bromide solution (1 M in benzene) was added, followed by 1 mL benzene. The resulting mixture was refluxed for 12.5 h. Work up and purification (vide supra) gave 102 mg (52%) of a 3.4:1 mixture (GC, 2% OV 101) of 198, 199, respectively.

Repetition of the above experiment led to an average yield of 56% and an average 198:199 ratio of 2.9:1.

Careful examination of the reaction by GC (5% OV 101) indicated the presence of traces of 202, 203, 204.

**Nickel Catalyzed Reaction of Vinylvagnesium Bromide with 74**

Normal catalyst reduction and alcohol deprotonation
were carried out with 1.308 g (2 mmol) of 65, 8.6 mL (24.1 mmol) of methylmagnesium iodide solution (2.8 M in ether), and 2.520 g (20 mmol) of 74 in 20 mL of benzene. Following the addition of 50 mL (60 mmol) of vinylmagnesium bromide solution (1.2 M in tetrahydrofuran) ether and tetrahydrofuran were distilled and replaced by benzene (50 mL net). After refluxing for 15 h, work up (petroleum ether, Na$_2$SO$_4$) and filtration of the resulting solution through alumina (activity I, basic), the mixture was distilled at atmospheric pressure to afford 2.162 g of a 0.27:0.27:0.27:0.19 mixture (86%) of 202, 203, 204, and benzene, identified by co-injection of authentic samples and by $^1$H and $^{13}$C NMR spectroscopy after purification by preparative GC (25% OV 101). $^{13}$C NMR:

![Chemical Structures](image)

l- [1-(l-Hexynyl)]-l-vinylcyclohexane, 205

Normal catalyst reduction and alcohol deprotonation were carried out with 654 mg (1 mmol) of 65, 3.8 mL (11.9 mmol) of methylmagnesium bromide solution (3.1 M in ether), and 1.260 g (10 mmol) of 74 in 10 mL of benzene. This mixture was transferred to a solution of 1-hexynylmagnesium bromide, prepared from 1.16 mL (10 mmol) of 1-hexyne, 3.2 mL
(9.9 mmol) of methylnitrogen bromide solution (3.1 M in ether), and 5 mL of benzene by refluxing for 2 hr. The resulting reaction mixture was refluxed for 61 h, followed by work-up (petroleum ether, MgSO₄), and distillation of solvents at atmospheric pressure. The residue was chromatographed on 55 g of 15% AgNO₃ on silica and eluted with petroleum ether and benzene mixtures to give 624 mg (33%) as an oil: IR: 1640 (m, C=C); ¹H NMR: 8 0.73-1.87 (m, 17, non-propargylic saturated H), 2.03-2.33 (m, 2, propargylic CH₂), 4.83 (dd, 1, J=2.9 Hz, E-vinyl CH₂ H), 5.17 (dd, 1, J=2.15 Hz, Z-vinyl CH₂ H), 5.63 (dd, 1, J=9.15 Hz, vinyl CH); ¹³C NMR:

![Chemical Structure](image)

MS: 190 (M⁺, 0.8), 105 (43), 93 (30), 92 (20), 91 (83), 81 (37), 80 (20), 79 (60), 78 (23), 77 (37), 67 (53), 66 (27), 65 (27), 57 (20), 55 (63), 54 (25), 53 (25), 43 (50), 42 (25), 41 (100), 40 (20); Anal. (calcd. for C₁₄H₂₂, C 88.35, H 11.65) C 88.20, H 11.66.

Careful examination of the reaction by GC (5% OV 101) indicated the presence of traces of 202, 203, 204.

5,5-Pentamethylene-1-trimethylsilyl-4-buten-1-ine, 207
Normal catalyst reduction and alcohol deprotonation were carried out with 654 mg (1 mmol) of $\text{654}$, 4.1 mL (12.1 mmol) of methylmagnesium bromide solution (2.95 M in ether), and 1.260 g (10 mmol) of $\text{74}$ in 5 mL of benzene. This mixture was transferred with the aid of 5 mL of benzene, to a solution of trimethylsilylethynylmagnesium bromide, prepared from 1.200 g (9.8 mmol) of trimethylsilylethylene solution (80% in tetrahydrofuran), 3.4 mL (10 mmol) of methylmagnesium bromide solution (2.95 M in ether), and 5 mL of benzene by stirring overnight at room temperature. Ether and tetrahydrofuran were distilled and replaced by benzene (25 mL net). The reaction mixture was refluxed for 72 h, followed by work-up (petroleum ether, MgSO$_4$), removal of solvents, and distillation of the residue to afford 623 mg (31%) $\text{207}$, b.p.=80–90°C (1 Torr). Further purification could be achieved by preparative GC (20% OV 101): IR: 2180(s, C≡C), 1665(w, C=C), 1250(s, Si-CH$_3$), 840(s, Si-CH$_3$); $^1$H NMR (CHCl$_3$ reference): δ 0.17(s, 9, Si(CH$_3$)$_3$), 1.57 (br s, 6, non-allylic CH$_2$), 2.13(br s, 4, allylic CH$_2$), 2.87 (d, 2, J=8 Hz, allylic propargylic CH$_2$), 5.10(br t, 1, J=8 Hz, olefinic CH); MS: 206(M$^+$,3), 191(27), 154(43), 153(37), 132(47), 131(47), 104(30), 77(37), 76(43), 73(50), 72(73), 67(33), 66(27), 59(97), 58(100), 55(27), 54(33), 53(20), 51 (27), 50(30), 45(30), 44(27), 43(43), 42(60), 41(33), 40(20); Anal. (calcd. for C$_{13}$H$_{22}$Si, C 75.64, H 10.75) C 75.41, H 10.49.

$\text{2-}(\beta \text{-o-Bromophenylethyl-})$cyclohexanone, $\text{211}$

To 6.407 g (35.8 mmol) of imine $\text{209}$ in 25 mL of tetrahydrofuran at 0°C was added dropwise 16.5 mL (38 mmol) of
methylmagnesium iodide solution (2.3 M in ether). The resulting mixture was heated gradually until refluxing, which was continued for 0.5 h at which time 9.500 g (36 mmol) of dibromide 21071 in 25 mL of tetrahydrofuran was added. After further refluxing for 1.5 h the reaction mixture was cooled to room temperature and 30 mL of concentrated hydrochloric acid and 10 mL of water were added. The resulting mixture was refluxed 3 h, cooled, and subjected to a normal work-up (CH₂Cl₂, Na₂SO₄), followed by removal of solvent, and distillation of the residue to afford 8.264 g (82%) 211, b.p.=135-150°C (0.2 Torr): IR: 1710(s, C=O), 1560(w), 1470(m), 1445(m, aromatic C=C), 750(s, 1,2-disubstituted aromatic); ¹H NMR (CDCl₃): 6 1.06-2.56(m, 11, saturated non-benzylic H), 2.70(t, 2, J=8 Hz, benzylic CH₂), 6.82-7.12(m, 1, aromatic H), 7.16(d, 2, J=4 Hz, aromatic H), 7.44(d, 1, J=8 Hz, aromatic H); ¹³C NMR: 24.8, 27.7, 29.5, 33.2, 33.7, 41.7(CH₂), 49.6(saturated CH), 123.9 (quaternary), 127.0(double peak), 129.9, 132.2(aromatic CH), 141.1(quaternary), 183.8(C=O); MS: 98(100), 83(20).


Repetition of the above experiment led to an average yield of 89%.

Z-2(Φ-o-Bromophenylethyl-)1-vinylcyclohexanol, 212

To 8.4 mL (10.1 mmol) of vinylmagnesium bromide solution (1.2 M in tetrahydrofuran) at 0°C was added dropwise 1.405 g (5 mmol) of 211 in 5 mL of tetrahydrofuran.
After warming to room temperature the mixture was stirred overnight, followed by cooling to 0°C, quenching through the slow addition of water, and normal work-up (CH₂Cl₂, Na₂SO₄). Removal of solvent and kugelrohr distillation of the residue at 145-150°C (0.1 Torr) furnished 1.226 g (80%) of 212: IR: 3580(m), 3480(m, OH), 1640(w, C=O), 1570(w), 1470(s), 1440(s, aromatic C=C), 750(s, 1,2-disubstituted aromatic); ¹H NMR: 0.73-2.17(m, 12, saturated non-benzylic H, OH), 2.17-3.00(m, 2, benzylic CH₂), 4.97(dd, 1, J=2,9 Hz, E vinyl CH₂ H), 5.13(dd, 1, J=2,18 Hz, Z vinyl CH₂ H), 5.73(dd, 1, J=9,18 Hz, vinyl CH), 6.77-7.27(m, 3, aromatic H), 7.40(d, 1, J=8 Hz, aromatic H); ¹³C NMR:

![Chemical Structure](image)

**MS:** 108(73), 93(20), 91(33), 90(23), 83(87), 82(33), 79(43), 78(23), 77(23), 70(47), 69(37), 67(27), 57(27), 55(100), 54(43), 43(40), 42(23), 41(67). Anal. (calcd. for C₁₆H₂₁BrO, C 62.14, H 6.85, Br 25.84) C 62.06, H 7.03, Br 25.60.

E, E-1,2,3,4a,9,10,10a-Octahydro-4a-(vinyl)phenanthrene, 213, 214
To 15.4 mL (20 mmol) of vinylmagnesium bromide solution (1.3 M in tetrahydrofuran) and 486 mg (20 mg atom) of magnesium powder at -78°C was added dropwise 5.520 g (20 mmol) of 211 in 20 mL of tetrahydrofuran. The resulting mixture was warmed to 0°C, at which temperature evidence of a reaction with magnesium became apparent. It then was warmed slowly to refluxing, which was maintained for 1 h, and a catalyst preparation, formed from 4.500 g (6.9 mmol) of 65 and 4.9 mL (13.7 mmol) of methylmagnesium iodide solution (2.8 M in ether) in 20 mL of benzene, was added with the aid of 30 mL more benzene. Tetrahydrofuran and ether then were distilled and replaced by benzene (85 mL net) and the reaction mixture was refluxed for 96 h. Cooling to room temperature was followed by work-up (petroleum ether, MgSO₄) and solvent removal to afford an oil which was filtered through alumina (activity I, basic) and eluted with petroleum ether. Solvent removal furnished 2 g of a clear, colorless oil, which was chromatographed on 100 g of 15% AgNO₃ on silica and eluted with heptane, to produce 806 mg (19%) of a partially resolved ca. 1:1 mixture of 213 and 214 (213 eluting first) as an oil. The latter could be distilled by kugelrohr at 90°C (0.2 Torr). 213: IR: 1630(m, C=O), 1600(w), 1495(m), 1450(s, aromatic C=O), 755(s, 1,2-disubstituted aromatic); ¹H NMR: δ 1.02-2.96(m, 13, saturated H), 4.38(dd, 1, J=2,17 Hz, Z vinyl CH₂ H), 4.92(dd, 1, J=2, 10 Hz, E vinyl CH₂ H), 5.74(dd, 1, J=10,17 Hz, vinyl CH), 6.88-7.32(m, 4, aromatic H); ¹³C NMR:
MS: 212(M⁺, 7), 169(23), 155(30), 144(37), 143(23), 142(27), 141(50), 130(30), 129(53), 128(40), 117(47), 116(20), 115(97), 110(20), 104(27), 95(23), 91(63), 87(50), 77(23), 71(20), 70(27), 69(57), 68(53), 67(43), 66(30), 59(27), 58(30), 57(47), 56(47), 55(60), 54(57), 45(27), 44(33), 43(70), 42(67), 41(100), 40(83); Anal. (calcd. for C₁₆H₂₀: C 90.51, H 9.49) C 90.61, H 9.44.

214: IR: 1630(m, C=O), 1600(w), 1485(m), 1450(s, aromatic C=O), 760(s, 1,2-disubstituted aromatic); ¹H NMR:

δ 1.00-3.10(m, 13, saturated H), 4.33(dd, 1, J=2.17 Hz, Z vinyl CH₂ H), 4.97(dd, 1, J=2.11 Hz, E vinyl CH₂ H), 6.17 (dd, 1, J=11.17 Hz, vinyl CH), 6.67-7.23m, 4, aromatic H); MS: 212(M⁺, 7), 183(27), 169(23), 155(33), 144(30), 143(43), 142(37), 141(73), 130(50), 129(73), 128(60), 127(20), 117(77), 116(23), 115(77), 97(20), 95(23), 91(47), 83(37), 82(27), 81(37), 79(20), 77(27), 71(27), 70(30), 69(63), 68(47), 67(37), 66(23), 57(53), 56(53), 55(77), 54(60), 53(20), 45(33), 44(43), 43(77), 42(67), 41(100), 40(83); Anal. (calcd. for C₁₆H₂₀: C 90.51, H 9.49) C 90.38, H 9.52.

Mixtures of 213 and 214 could be separated also by
preparative GC (25% OV 101).

From the same silver nitrate-impregnated silica column yielding 213 and 214 there could be obtained 219 and 218, eluting in that order before 213, 214. 219: IR: 1600(w), 1485(m), 1445(m, aromatic C=C), 750(m), 700(w, mono-substituted aromatic); $^1$H NMR: δ 0.80-2.00(m, 12, non-benzylic saturated CH$_2$CH), 1.25(d, 3, J=6 Hz, CH$_3$), 2.42-3.30(m, 2, benzylic CH$_2$), 6.80-7.66(m, 5, aromatic H); $^{13}$C NMR:

![Chemical structure](image)

218: IR: 1605(w), 1495(m), 1455(s, aromatic C=C), 750(m), 700(s, mono-substituted aromatic); $^1$H NMR: δ 1.10-2.94(m, 16, non-benzylic saturated CH$_2$CH), 1.54(app t, 6, J=6 Hz, CH$_3$), 2.50(t, 4, J=8 Hz, benzylic CH$_2$), 5.12(q, 1, J=6 Hz, olefinic CH of one isomer), 5.14(q, 1, J=6 Hz, olefinic CH of one isomer), 6.90-7.34(m, 10, aromatic H); $^{13}$C NMR: 12.6(CH$_3$), 21.4, 23.6, 25.9, 27.9, 28.6, 31.7, 32.8, 33.7, 34.0(multiple peak), 35.2(CH$_2$), 44.1(saturated CH), 114.5, 116.6, 125.3, 128.0(multiple peak)(sp$^2$ CH), 141.6, 141.9, 142.7, 142.8 (quaternaries).

β -Allylindole, 221

Normal catalyst reduction and indole and alcohol
deprotonations were carried out with 654 mg (1 mmol) of 65, 15 mL (42 mmol) of methylmagnesium iodide solution (2.8 M in ether), 1.170 g (10 mmol) of indole, and 2.04 mL (30 mmol) of allyl alcohol in 10 mL of ether. The resulting mixture was refluxed for 22 h after which it was cooled, worked up (CH₂Cl₂, Na₂SO₄) and filtered through a short silica column. The solvents were removed and the residue was chromatographed carefully on silica and eluted with CHCl₃, to give 983 mg (59%) of 221: IR: 3420(s, NH), 1640(m, C=C); ¹H NMR: δ 3.50 (d, 2, J=6 Hz, allylic CH₂), 4.96-5.30(m, 2, olefinic CH₂), 6.06(ddt, 1, J=6,10,16 Hz, olefinic CH), 6.82-6.96(m, 1, indole C2 H), 6.96-7.38(m, 3, aromatic H), 7.46-8.10(m, 2, NH, aromatic H); ¹³C NMR: 29.8(allylic CH), 111.1(CH), 115.1(olefinic CH₂), 119.0, 119.2, 121.7, 121.9(CH), 127.4, 136.4, 137.3(quaternaries); MS: 157(M⁺,50), 156(40), 130(100), 129(30), 128(27), 77(63), 76(33), 64(20), 63(27), 51(33), 50(23); UV(hexane): 265 nm (ε 5600).

The reaction could also be performed in benzene.

**Nickel Catalyst Treatment of N- Allylindole, 222**

Normal catalyst reduction was carried out with 654 mg (1 mmol) of 65 and 0.7 mL (2 mmol) of methylmagnesium iodide solution (2.8 M in ether). To this was added 1.478 g (9.4 mmol) of 222 in 10 mL of benzene. The resulting reaction mixture was refluxed for 12 h, at which time GC (5% OV 101) indicated largely 222 and a small amount of indole to be present.
Nickel-catalyzed Reaction of Methylmagnesium Iodide with 222

Normal catalyst reduction was carried out with 654 mg (1 mmol) of 65 and 4.3 mL (12 mmol) of methylmagnesium iodide solution (2.8 M in ether) in 15 mL of benzene. To this mixture was added 1.570 g (10 mmol) of 222 in 10 mL of benzene and the reaction mixture was refluxed overnight and worked up (CH₂Cl₂, Na₂SO₄). The solvents were removed, and the residue chromatographed on 30 g of silica, eluting with petroleum ether-benzene mixtures, to give 1.104 g (94%) of indole.

Methylmagnesium Bromide Treatment of 222

A mixture of 785 mg (5 mmol) of 222 and 2.4 mL (6 mmol) of methylmagnesium bromide solution (2.5 M in ether) in 10 mL of benzene was refluxed 40 h and worked up (CH₂Cl₂, Na₂SO₄) to give 571 mg (73%) of recovered 222. GC (5% OV 101) indicated no indole to be present.

Nickel-catalyzed Reaction of Phenylmagnesium Bromide with 222

Normal catalyst reduction was carried out with 1.308 g (2 mmol) of 65 and 1.6 mL (4 mmol) of methylmagnesium bromide solution (2.5 M in ether). To this was added 3.140 g (20 mmol) of 222 in 10 mL of benzene followed by 10 mL (22 mmol) of phenylmagnesium bromide solution (2.2 M in ether). After the mixture had been refluxed for 41 h and
worked up (CH$_2$Cl$_2$, Na$_2$SO$_4$), the extract was filtered through silica and the solvents distilled at atmospheric pressure. The residue was distilled further to yield a fraction, b.p.=120-150$^\circ$C (151 Torr), whose $^1$H NMR spectrum indicated it to contain allylbenzene, 67, identical with an authentic sample. The non-volatile material from this latter distillation was chromatographed on 100 g silica, eluting with petroleum ether-benzene mixtures, to yield indole.

$\text{2-(3,3-Dimethylpropen-3-yl)-1Hindole, 225, 3-}(1,1\text{-dimethylpropen-3-yl)-1Hindole, 226}$

Normal catalyst reduction was carried out with 585 mg (0.9 mmol) of 65 and 6 mL (16.8 mmol) of methylmagnesium iodide solution in 15 mL of benzene. Ether was distilled and after cooling to 0$^\circ$C, 574 mg (4.9 mmol) of indole in 3 mL of benzene was added, followed shortly thereafter by 1.05 mL (10 mmol) of 3,3-dimethylpropen-3-ol. The resulting mixture was refluxed 61 h, after which it was cooled and worked up (CH$_2$Cl$_2$, Na$_2$SO$_4$). The resulting solution was filtered through a short silica column and the solvents removed to give an oil. Purification by preparative TLC (silica) and elution with petroleum ether-benzene (1:1) led to 333 mg (58%) of recovered indole and 111 mg (29% based on consumed indole) of a 3:1:1 mixture (GC, 2% OV 101) of 225 and 226, respectively. 225: IR: 3420(s, NH), 1640(m, C=O), 1380(s), 1360(s, C (CH$_3$)$_2$); $^1$H NMR:

$\delta$ 1.45(s, 6, CH$_3$), 4.83-5.20(m, 2, vinyl CH$_2$), 6.03(dd, 1, J=11,18 Hz, vinyl CH), 6.70(d, 1, J=3 Hz, indole C2 H),
6.77-7.17 (m, 3, aromatic H), 7.20-7.67 (m, 2, NH, aromatic H); MS: 185 (M^+, 23), 170 (50), 143 (23), 130 (53), 121 (40), 117 (67), 115 (23), 91 (23), 84 (20), 83 (33), 81 (40), 77 (63), 76 (27), 71 (23), 70 (27), 69 (100), 68 (67), 67 (27), 57 (30), 56 (30), 55 (40), 54 (30), 43 (50), 42 (40), 41 (97), 40 (70); UV (hexane): 265 nm (ε 4800); Anal. (calcd. for C_{13}H_{15}N, C 84.28, H 8.16, N 7.56) C 84.10, H 8.28, N 7.49. 226: IR: 3420 (s, NH), 1670 (w, C=C); \(^1\)H NMR: 5 1.70 (s, 6, CH\(_3\)), 3.37 (d, 2, J=8 Hz, allylic CH\(_2\)), 5.33 (br t, 1, J=8 Hz, olefinic OH), 6.70 (br s, 1, C2 H), 6.80-7.13 (m, 3, aromatic H), 7.20-7.67 (m, 2, NH, aromatic H); MS: 185 (M^+, 30), 170 (100), 155 (30), 154 (27), 143 (33), 130 (27), 128 (23), 115 (23), 83 (23), 77 (47), 76 (23), 69 (33), 68 (30), 41 (40), 40 (40); UV(hexane): 268 nm (ε 3200).

Mixtures of 225-226 could be separated by chromatography on 15% AgNO\(_3\) on silica and eluted with benzene-ether mixtures, to give first 226, followed by 225 as an oil which could be distilled in a kugelrohr at 100°C (0.5 Torr).

Reproducibility in this experiment could only be achieved through the use of the freezing technique of Felkin, et al.\(^{16b}\) in setting up the reaction.

2-(allyl)-3-methyl-indole, 228

Normal catalyst reduction and indole and alcohol deprotonations were carried out with 654 mg (1 mmol) of 65, 15 mL (42 mmol) of methylmagnesium iodide solution (2.8 M in ether), 1.310 g (10 mmol) of skatole, and 2.04
mL (30 mmol) of allyl alcohol in 10 mL of benzene. Ether was distilled, 10 mL of benzene added, and the reaction mixture was refluxed for four days. At this time the reaction mixture was cooled to 0°C, 15 mL of 1 N aqueous hydrochloric acid in 10 mL of tetrahydrofuran was added, and after 0.5 h a normal work-up (CH₂Cl₂, Na₂SO₄) was performed. After solvent removal the residue was chromatographed carefully on silica and eluted with carbon tetrachloride to yield 121 mg (9%) of recovered skatole and 244 mg (16% based on consumed skatole) of 22875 as an oil which could be distilled by kugelrohr at 100-110°C (1 Torr): IR: 3410(s, NH), 1635(m, C=O); ¹H NMR:

δ 2.13(s, 3, CH₃), 3.24(d, 2, J=6 Hz, allylic CH₂), 4.80-5.20(m, 2, vinyl CH₂), 5.53-6.03(m, 1, vinyl CH), 6.67-7.63 (m, 5, NH, aromatic H); MS: 171(M⁺,100), 170(47), 156(43), 154(23), 144(23), 130(47), 129(47), 128(33), 115(30), 77(67), 76(23), 65(23), 63(30), 51(60), 50(30), 43(27), 41(40);
Anal. (calcd. for C₁₂H₁₃N, C 84.17, H 7.65, N 8.18) C 84.07, H 7.81, N 8.27.

3-Phenylcyclohexene, 234

Normal catalyst reduction and alcohol deprotonation were carried out with 654 mg (1 mmol) of 65, 4.8 mL (12 mmol) of methylmagnesium bromide solution (2.5 M in ether) and 0.98 mL (10 mmol) of 2-cyclohexenol. Following the addition of 9 mL (19.8 mmol) of phenylmagnesium bromide solution (2.2 M in ether) ether was distilled and replaced
by benzene (17 mL net). After refluxing 15 h, the reaction mixture was cooled and worked up (petroleum ether, MgSO₄). The resulting solution was filtered through alumina (activity I, basic), and the solvents removed to provide 1.413 g of a mixture of biphenyl (23%) and 234 ⁷⁶ (77% by ¹H NMR). The yield of 234 was 69%: ¹H NMR: δ 1.33-2.23 (m, 6, CH₂), 3.17-3.50 (m, 1, allylic benzylic CH), 5.63-5.83 (m, 2, olefinic CH), 6.87-7.60 (m, 5, aromatic H).

3-Phenyl-1,2-dimethylcyclohexene, 237, Bis-1,2-Dimethyl-cyclohexenyl, 238

Normal catalyst reduction was carried out with 654 mg (1 mmol) of 65 and 4.8 mL (12 mmol) of methylmagnesium bromide solution (2.5 M in ether). This mixture was cooled to 0°C and 1.15 mL (10 mmol) of 3-methyl-2-cyclohexenone, 235, was added dropwise. After warming to room temperature and stirring for 0.5 h, 9 mL (19.8 mmol) of phenylmagnesium bromide solution (2.2 M in ether) was added and the ether was distilled and replaced by benzene (12 mL net). After refluxing for 41 h, the reaction mixture was cooled, worked up (petroleum ether, MgSO₄) and the resulting solution filtered through alumina (activity I, basic). The solvents were removed and the residue was chromatographed on 30 g alumina (activity I, basic) and eluted with petroleum ether, to furnish 234 mg (21%) of 238 (ca. 1:1 mixture of diastereomers) as an oil which could be distilled by kugelrohr at 80-90°C (0.1 Torr), and 117 mg (6%) of 237 as an oil which could be distilled by kugelrohr at 80-90°C (0.1 Torr).
IR: 1680 (w, C=C), 1610 (m), 1510 (s), 1460 (s, aromatic C=C), 780 (s), 720 (s, mono-substituted aromatic); ¹H NMR: 6 0.73-2.53 (m, 6, saturated CH₂), 1.33 (s, 3, non-allylic CH₃), 1.73 (s, 3, allylic CH₃), 5.40 (br s, 1, olefinic CH), 6.90-7.43 (m, 5, aromatic H); ¹³C NMR: 19.6 (CH₂), 23.9, 29.6 (CH₃), 30.0, 38.7 (CH₂), 39.6 (saturated quaternary), 125.2, 126.4 (double peak), 127.7 (double peak), 129.4 (sp² CH), 133.4, 150.0 (sp² quaternaries); MS: 186 (M⁺, 14), 171 (93), 149 (37), 143 (27), 129 (36), 128 (24), 115 (24), 109 (27), 105 (20), 93 (24), 91 (100), 77 (25), 67 (36), 57 (31), 55 (36), 43 (63), 41 (63); Anal. (calcd. for C₁₄H₁₈, C 90.26, H 9.74) C 90.08, H 9.82.

238: IR: 1680 (w, C=C); ¹H NMR: 0.87 (s, 3, non-allylic CH₃), 0.90 (s, 3, non-allylic CH₃), 1.10-2.23 (m, 12, CH₂), 1.60 (s, 6, allylic CH₃), 5.23 (br s, 2, olefinic CH); ¹³C NMR: 20.0, 20.2, 21.8, 22.0 (CH₂), 24.2, 24.3 (CH₃), 29.9, 30.0 (double peak) (CH₂, CH₃), 40.0, 40.7 (saturated quaternaries), 127.6, 128.5 (CH), 132.2, 132.9 (olefinic quaternaries); MS: 218 (M⁺, 0.3), 111 (32), 109 (100), 67 (47), 43 (24), 41 (23); Anal. (calcd. for C₁₆H₂₆, C 88.00, H 12.00) C 87.91, H 11.82.

Repetition of the above experiment led to the isolation of 237 in 7% yield.

Bis-1,3-Dimethylcyclohexenyl, 238, from the Nickel-catalyzed Reaction of Methylmagnesium Bromide and 3-Methyl-2-cyclohexene-
one

Normal catalyst reduction was carried out with 1.308 g (2 mmol) of 65 and 26 mL (65 mmol) of methylmagnesium bro-
mide solution (2.5 M in ether). After cooling to 0°C, 2.3 mL (20 mmol) of 3-methyl-2-cyclohexenone, 235, was added dropwise. The resulting mixture was warmed to room temperature, and the ether distilled and replaced by benzene (22 mL net). After refluxing for six days, the reaction mixture was cooled and worked up (petroleum ether, MgSO₄). The resulting solution was filtered through alumina (activity I, basic) and the solvents removed. Chromatography of the residue on 40 g of alumina (activity I, basic) and elution with petroleum ether led to 578 mg (27%) of 238.

**Nickel-catalyzed Reaction of Vinylmagnesium Bromide with Tetradeuterio Alcohol 239 (Water Work-up).**

A reaction analogous to that involving 74 (vide supra) was performed with 2.600 g (20 mmol) of tetradeuterio alcohol 239 (from vinylmagnesium bromide addition to 2,2,6,6-tetradeuteriocy clohexanone). ¹³C NMR established the products to be 240 (signals at 25.7, 129.3, and 135.8 ppm in 202 absent), 241 (signals at 32.6 and 41.7 ppm in 203 absent), 243 (signal at 12.3 ppm in 204 manifested as a singlet at 12.5 ppm, signals at 28.2 and 37.1 ppm in 204 absent).

**Nickel-catalyzed Reaction of Vinylmagnesium Bromide with Tetradeuterio Alcohol 239 (Deuterium Oxide Work-up)**

A reaction analogous to that involving 74 (vide supra) was performed with 2.600 g (20 mmol) of tetradeuterio alcohol 239 except that the reaction was quenched with 5 mL of
1 M trideuteriophosphoric acid in deuterium oxide. $^{13}$C NMR indicated 240, 241, and 242 (signal at 12.3 ppm in 204 manifested as a triplet at 12.1 ppm, J = 20 Hz, signals at 28.2 and 37.1 ppm in 204 absent) to be present.

**Attempted Formation and Thermolysis of Bis-\(\text{H}^-\) -allyl 248**

To 612 mg (25.2 mgat.) of magnesium in 1.5 mL of ether was added dropwise 2.189 g (11.6 mmol) of \(\beta\) -bromoethylidenecyclohexane\(^77\) in 13.5 mL of ether such that the temperature was maintained near the solvent boiling point. The mixture was then stirred overnight at room temperature, at which time hydrolysis of an aliquot and analysis (GC, 5% OV 101) indicated the presence of 202, 203, 204, with 204 present in slightly greater amount than 203. The Grignard reagent solution was transferred with the aid of 5 mL of ether to 1.269 g (5.8 mmol) of anhydrous nickel dibromide in 20 mL of ether maintained at -78°C. The resulting mixture was warmed to 0°C, then to room temperature, and finally was refluxed overnight. The solvent was exchanged for benzene (30 mL net) by distillation and the resulting mixture refluxed overnight. At no time was there evidence of reaction between the Grignard reagent and the nickel salt, which remained as an insoluble solid through all operations.

**1-Phenyl-1-(propen-2-yl)cyclohexane, 251**

Normal catalyst reduction and alcohol deprotonation were carried out with 327 mg (0.5 mmol) of 65, 2.5 mL
(6.3 mmol) of methylmagnesium bromide solution (2.5 M in ether), and 700 mg (5 mmol) of 1-(propen-2-yl)cyclohexan-1-ol,\textsuperscript{78} \textsuperscript{250}. To this mixture was added 6.8 mL (15 mmol) of phenylmagnesium bromide solution (2.2 M in ether). Ether was distilled and replaced by benzene (14 mL net) and the reaction mixture refluxed for 24 h. After cooling the reaction was worked up (petroleum ether, MgSO\textsubscript{4}). The resulting solution was filtered through alumina (activity I, basic) and the solvents removed. The residue was chromatographed on 50 g of 15\% AgNO\textsubscript{3} on silica and eluted with petroleum ether to furnish 307 mg of pure \textsuperscript{251} as an oil as well as 617 mg of a mixture of \textsuperscript{251} (48\%) and biphenyl (52\% by \textsuperscript{1}H NMR). The total yield of \textsuperscript{251} was 63\%: IR: 1640(m, C=C), 1605(m), 1500(s), 1455(s, aromatic C=C), 770(s), 710 (s, mono-substituted aromatic); \textsuperscript{1}H NMR: \delta 1.20-1.77(br s, 6, saturated CH\textsubscript{2}), 1.43(s, 3, CH\textsubscript{2}), 1.77-2.30(m, 4, saturated CH\textsubscript{2}), 4.87(m, 1, olefinic CH\textsubscript{2} H), 4.93(br s, 1, olefinic CH\textsubscript{2} H), 6.97-7.40(m, 5, aromatic H); \textsuperscript{13}C NMR:
MS: 200(M⁺,17), 143(29), 129(47), 128(21), 118(40), 117(28), 115(27), 91(100), 81(20), 77(23), 55(20), 51(20), 41(47); m/e (calcd. for C₁₅H₂₀, 200.1565) 200.1570.

L-(α-Styryl)-1-phenylcyclohexane, 255

Normal catalyst reduction and alcohol deprotonation were carried out with 327 mg (0.5 mmol) of 65, 2 mL (5.9 mmol) of methylmagnesium bromide solution (2.95 M in ether), and 780 mg (5 mmol) of L-(α-methoxyvinyl)cyclohexanol, 79 254. Following the addition of 10.8 mL (15.1 mmol) of phenylmagnesium bromide solution (1.4 M in ether), ether was distilled and replaced by benzene (13 mL net), and the reaction mixture refluxed 27 h. After cooling and work-up (petroleum ether, MgSO₄) the solvents were removed and the residue chromatographed on 30 g of 15% AgNO₃ on silica and eluted with petroleum ether-benzene mixtures, to afford 600 mg (46%) 255 as an oil which could be distilled by kugelrohr at 120-125°C (0.05 Torr): IR: 1620(m,C=O), 1600(m), 1490(s), 1450(s, aromatic C=C), 755(s), 700(s, mono-substituted aromatic); ¹H NMR: δ 1.07-2.27(m, 10, saturated CH₂), 5.07(d, 1, J=2 Hz, olefinic CH₂ H), 5.27(d, 1, J=2 Hz, olefinic CH₂ H), 6.40-6.70(m, 2, aromatic H), 6.77-7.53(m, 8, aromatic H); ¹³C NMR:
MS: 262(M⁺, 7), 159(33), 91(100), 90(53), 81(27); Anal. (calcd. for C20H22, C 91.55, H 8.45) C 91.30, H 8.57.

When this experiment was repeated with 3.6 mL (5 mmol) of phenylmagnesium bromide solution (1.4 M in ether), GC (5% OV 101) at the end of 26 h indicated the presence of a ca. 1:1 mixture of 254 and 255. At no time during the reaction did GC indicate components other than 254, 255, biphenyl, and triphenylphosphine.

1-(Propen-2-yl)cyclohexan-1-ol, 250

Normal catalyst reduction and alcohol deprotonation were carried out with 654 mg (1 mmol) of 65, 18 mL (53.1 mmol) of methylmagnesium bromide solution (2.95 M in ether), and 1.560 g (10 mmol) of 254. Ether was distilled and replaced by benzene (30 mL net) and the resulting reaction mixture refluxed for 44 h. At this time it was cooled, 1 N aqueous hydrochloric acid added and a normal work up performed (CH₂Cl₂, Na₂SO₄). Removal of the solvents and distillation of the residue, b.p.=80–90°C (10 Torr), led to
1.005 g (72%) 250: IR: 3440(s, OH), 1640(m, C=O);
\(^1\)H NMR: \( \delta \) 0.77-2.33(m, 10, saturated CH\(_2\)), 1.53(s, 3, CH\(_2\)), 1.73(s, 1, CH), 4.67(m, 1, olefinic CH H), 4.90(s, 1, olefinic CH\(_2\) H); MS: 140(M\(^+\),3), 109(37), 108(30), 98(20), 97(93), 96(93), 84(30), 83(23), 81(27), 80(27), 79(30), 78(20), 69(57), 68(40), 55(50), 54(40), 43(97), 42(93), 41(100), 40(90).

Isolation and subjection of 250 to the conditions of the above reaction led only to its recovery.

1-Phenylcyclohexene, 261, from 1-Methoxycyclohexene, 260

Normal catalyst reduction was carried out with 654 mg (1 mmol) of 65 and 0.68 mL (2 mmol) of methylmagnesium bromide solution (2.95 M in ether) in 10 mL of benzene. Following the addition of 10 mL (20 mmol) of phenylmagnesium bromide solution (2 M in ether), ether was distilled and replaced by benzene (35 mL net), and 1.120 g (10 mmol) 1-methoxycyclohexene, \(^{80,81} 260\), added. The resulting reaction mixture was refluxed for 40 h, at which time it was cooled and worked up (petroleum ether, MgSO\(_4\)). The resulting solution was filtered through alumina (activity I, basic), and the solvents removed. The residue was chromatographed on 50 g of 15% AgNO\(_3\) on silica and eluted with petroleum ether, to give 1.118 g (71%) 261: \(^{82} \) \(^1\)H NMR: \( \delta \) 1.37-2.57(m, 8, CH\(_2\)), 5.87-6.10(m, 1, olefinic CH), 6.90-7.57(m, 5, aromatic H).

1-Methoxy-4-t-butyl-1-cyclohexene, 262
Distillation of 1,1-dimethoxy-4-tert-butylcyclohexane\textsuperscript{83} from a catalytic amount of di-isopropylethylammonium tosylate initially at atmospheric pressure to remove methanol and then at reduced pressure afforded 262,\textsuperscript{84} b.p. = 125\textdegree C (50 Torr): IR: 1670(s, C=O), 1390(s), 1370(s, C(CH\textsubscript{3})\textsubscript{3}); \textsuperscript{1}H NMR: \delta 0.87(s, 9, C(CH\textsubscript{3})\textsubscript{3}), 1.00-2.23(m, 7, saturated CH, CH\textsubscript{2}), 3.37(s, 3, OCH\textsubscript{3}), 4.37-4.53(m, 1, olefinic CH); MS: 168(M\textsuperscript{+},13), 153(36), 111(37), 84(100), 83(20), 81(21), 80(23), 79(45), 69(27), 67(28), 58(32), 57(67), 55(27), 54(21), 45(21), 43(31), 41(93).

\textit{1-Phenyl-4-tert-butyl-1-cyclohexene}, 263

Normal catalyst reduction was carried out with 327 mg (0.5 mmol) of 65 and 0.4 mL (1 mmol) of methylmagnesium bromide solution (2.5 M in ether). After the addition of 4.5 mL (9.9 mmol) of phenylmagnesium bromide solution (2.2 M in ether), ether was distilled and replaced by benzene (13 mL net), and 840 mg (5 mmol) of 262 added. The resulting mixture was refluxed for 34 h, cooled, worked up (petroleum ether, MgSO\textsubscript{4}) and filtered through alumina (activity I, basic), and the solvents removed. \textsuperscript{1}H NMR indicated the residue (1.004 g) to be a mixture of biphenyl (20%) and 263\textsuperscript{85} (80%). The yield of 263 was 75%: \textsuperscript{1}H NMR: \delta 0.90(s, 9, C(CH\textsubscript{3})\textsubscript{3}), 1.07-2.53(m, 7, saturated CH, CH\textsubscript{2}), 5.90-6.07 (br s, 1, olefinic CH), 7.00-7.57(m, 5, aromatic H).

\textit{1-Methyl-4-tert-butylcyclohexene}, 264
Normal catalyst reduction was carried out with 654 mg (1 mmol) of 65 and 8.8 mL (19.4 mmol) of methylmagnesium bromide solution (2.5 M in ether). Following distillation of the ether and replacement by benzene (15 mL net), 1.680 g (10 mmol) of 262 was added and the resulting mixture refluxed for 158 h. After cooling, work-up (petroleum ether, MgSO₄), and filtration through alumina (activity I, basic), the solvents were removed to furnish 896 mg (59%) 264:

\[ ^1H \text{NMR: } 8 \] 0.87(s, 9, C(CH₃)₃), 1.00-2.17(m, 7, saturated CH, CH₂), 1.60(s, 3, allylic CH₂), 5.20-5.43(br s, 1, olefinic CH).

1-Phenylcyclohexene, 261, from 1-trimethylsilyloxy cyclohexene, 265

Normal catalyst reduction was carried out with 327 mg (0.5 mmol) of 65 and 0.4 mL (1 mmol) of methylmagnesium bromide solution (2.5 M in ether). After the addition of 4.5 mL (9.9 mmol) of phenylmagnesium bromide solution (2.2 M in ether), ether was distilled and replaced by benzene (20 mL net), and 850 mg (5 mmol) of 265 added. The resulting mixture was refluxed for 25 h, cooled, worked up (CH₂Cl₂, Na₂SO₄), and the solvents removed. Chromatography of the residue on 30 g of silica and elution with hexane led to 240 mg (30%) of 261.

E,Z-4-Phenyl-3-heptene, 273, 274

Normal catalyst reduction was carried out with 654 mg (1 mmol) of 65 and 0.8 mL (2 mmol) of methylmagnesium bro-
mide solution (2.5 M in ether). Following the addition of 9 mL (19.8 mmol) of phenylmagnesium bromide solution (2.2 M in ether), ether was distilled and replaced by benzene (15 mL net), and 1.280 g (10 mmol) of 4-methoxy-3-heptene (E/Z=1:3.3 from integration of $^1$H NMR OMe signals and inspection of $^1$H NMR olefinic CH resonances; E: § 4.40, Z: § 4.23) added. The resulting reaction mixture was refluxed for 39 h, cooled and worked up (petroleum ether, MgSO$_4$). The solution was filtered through alumina (activity I, basic), and the solvents removed to yield 1.690 g of a mixture of 273, 274 (89%) and biphenyl (11% by $^1$H NMR). The yield of 273, 274 was 86%. $^1$H NMR indicated the E/Z (274/273) ratio to be 3:1:1. $^1$H NMR: § 0.70-1.63 (m, 32.8, non-allylic CH$_2$, CH$_3$), 1.73-2.63 (m, 16.4, allylic CH$_2$), 5.37 (t, 1, J=6 Hz, Z olefinic CH), 5.57 (t, 3.1, J=6 Hz, E olefinic CH), 6.93-7.73 (m, 20.5, aromatic H).

Equilibration$^{62}$ of E,Z-4-Phenyl-3-heptene, 273, 274

To a glass tube sealed at one end there were added 273-274 (E/Z=3.1:1), a drop of thiophenol, and a spatula tip of AIBN. After flushing with argon, the tube was evacuated, sealed and placed in an oven at approximately 130°C for 3 h. At this time the tube was cooled and opened and the contents taken up in petroleum ether, washed with aqueous sodium hydroxide solution, water and dried (MgSO$_4$). The solvents were removed to yield 273, 274. The E/Z ratio (273/274) was 1.3:1 by $^1$H NMR analysis.
E,Z-1-Phenyl-1-heptene, 277, 278

Normal catalyst reduction was carried out with 654 mg (1 mmol) of 65 and 0.8 mL (2 mmol) of methylmagnesium bromide solution (2.5 M in ether). Following the addition of 9 mL (19.8 mmol) of phenylmagnesium bromide solution (2.2 M in ether), ether was distilled and replaced by benzene (16 mL net), and 1.280 g (10 mmol) of 1-methoxy-1-heptene\(^{80}\) (E/Z=1.3:1 from integration of \(^1\)H NMR olefinic C2 H signals; E: \(\delta\) 4.57, Z: \(\delta\) 4.20) added. The resulting reaction mixture was refluxed for 16 h, cooled and worked up (petroleum ether, MgSO\(_4\)). The solution was filtered through alumina (activity I, basic), and the solvents removed. The residue was chromatographed on 50 g of alumina (activity I, basic) and eluted with petroleum ether to give 1.367 g (79%) of a mixture of 277, 278.\(^{90}\) \(^{13}\)C NMR indicated the E/Z (277/278) ratio to be 1.7:1. \(^1\)H NMR: \(\delta\) 0.70-1.10(m, 3, CH\(_3\)), 1.13-1.70(m, 6, non-allylic CH\(_2\)), 2.00-2.43(m, 2, allylic CH\(_2\)), 5.40-6.47(m, 2, olefinic CH), 6.87-7.37(m, 5, aromatic H); \(^{13}\)C NMR:
Equilibration of this mixture analogously to 273, 274 led exclusively to 277 by $^{13}$C NMR.

**E,Z-2-Octene, 279, 280**

Normal catalyst reduction was carried out with 1.308 g (2 mmol) of 65 and 18 mL (45 mmol) of methylmagnesium bromide solution (2.5 M in ether). Ether was distilled and replaced by benzene (20 mL net) and 2.511 g (19.6 mmol) of 1-methoxy-1-heptene (E/Z=1.3:1) added. The resulting reaction mixture was refluxed for 15 h, cooled and worked up (petroleum ether, MgSO$_4$). The solution was filtered through alumina (activity I, basic), and the solvents distilled at atmospheric pressure. The residue was distilled to give 1.987 g of a mixture of benzene (23%) and 279, 280 by $^1$H NMR (77%), b.p. = 65-100$^\circ$C (150 Torr). The yield of 279, 280 was 70%. $^{13}$C NMR indicated the E/Z (279/280) ratio to be 1.4:1. $^1$H NMR: δ 0.63-2.23 (m, 14, saturated CH$_2$, CH$_3$), 5.23-5.60 (m, 2, olefinic CH); $^{13}$C NMR:

![Chemical structure diagram](attachment:image)

Z-5-Phenylpent-4-en-1-ol, 282, from the Nickel-catalyzed Reaction of Phenylmagnesium Bromide with Dihydropyran

Normal catalyst reduction was carried out with 327 mg
(0.5 mmol) of 65 and 0.34 mL (1 mmol) of methylmagnesium bromide solution (2.95 M in ether). Following the addition of 7.2 mL (10.1 mmol) of phenylmagnesium bromide solution (1.4 M in ether), ether was distilled and replaced by ben- zene (11 mL net). After the addition of 460 uL (5 mmol) of dihydropyran, the mixture was refluxed 24 h, at which time 920 uL (10 mmol) dihydropyran was added. Refluxing a fur- ther 14 h was followed by cooling, work-up (CH₂Cl₂, Na₂SO₄), removal of the solvents, and kugelrohr distillation (100°C (0.1 Torr)) of the residue to provide 1.373 g of a mixture of 282 (75%), identical to independently prepared material and biphenyl (25%). The yield of 282 was 63%. 282:
IR: 3330(s, OH), 1610(m, C=C and aromatic C=O), 1505(s), 1460(s, aromatic C=C), 1080(s, C-O), 780(s), 720(s, mono- substituted aromatic); ¹H NMR: δ 1.40-1.97(m, 2, O2 H), 2.17-2.67(m, 2, O3 H), 2.93(br s, 1, OH), 3.50(t, 2, J=6 Hz, O1 H), 5.57(dt, 1, J=6,12 Hz, C4 H), 6.37(br d, 1, J=12 Hz, O5 H), 7.03-7.47(br s, 5, aromatic H); ¹³C NMR:

MS: 162(M⁺,22), 144(25), 143(22), 129(97), 128(36), 118(22), 117(57), 116(23), 115(78), 105(20), 104(27), 92(21), 91(100),
85(61), 77(28), 67(24), 65(22), 57(41), 55(31), 51(26), 43(48), 41(54). Anal. (calcd. for C_{11}H_{14}O, C 81.44, H 8.70) C 81.28, H 8.84.

Equilibration\textsuperscript{62} of 282, analogously to 273, 274, led to E-5-phenylpent-4-en-1-ol \textsuperscript{92} \textsuperscript{1}H NMR: \delta 1.40-1.90 (m, 2, C2 H), 2.10-2.43 (m, 2, C3 H), 3.17 (br s, 1, OH), 3.57 (t, 2, J=6 Hz, Cl H), 5.83-6.50 (m, 2, olefinic CH), 6.83-7.67 (m, 5, aromatic H); \textsuperscript{13}C NMR:

![Structural diagram]

E, Z-4-Hexen-1-ol, 283, 284

Normal catalyst reduction was carried out with 654 mg (1 mmol) of 65 and 4.1 mL (12.1 mmol) of methylmagnesium bromide solution (2.95 M in ether). Ether was distilled and replaced by benzene (14 mL net). After the addition of 1.84 mL (20 mmol) of dihydropyran the reaction mixture was refluxed for 22 h, whereupon 0.92 mL (10 mmol) of dihydropyran was added and refluxing continued for 9 h. At this time the reaction was cooled, worked up (CH\textsubscript{2}Cl\textsubscript{2}, Na\textsubscript{2}SO\textsubscript{4}), and the solvents removed. The residue could be distilled by kugelrohr at water pump pressure and 120°C to provide 741 mg (73%) of a 3:1:1 mixture of 283, 284 \textsuperscript{92} by \textsuperscript{13}C NMR: IR: 3360(s, OH), 1660(m, C=C), 1060(s, C-O), \textsuperscript{1}H NMR: \delta 1.33-
1.83 (m, 5, CH₂, C₂ H), 1.83–2.43 (m, 2, allylic CH₂), 3.53 (t, 2, J=6 Hz, Cl H), 3.67 (s, 1, OH), 5.13–5.67 (m, 2, olefinic CH); ¹³C NMR:

Equilibration⁶² of 283–284, analogously to 273–274, led to a 1:2.9 283–284 ratio by ¹³C NMR.

4-Penten-1-yl Acetate, 285, 2-4-Hepten-1-yl Acetate, 286, from 65

To 1.635 g (2.5 mmol) of 65 was added 15 mL (25 mmol) of ethylmagnesium bromide solution (1.66 M in ether). Ether was distilled and replaced by benzene (30 mL net) and 1.84 mL (20 mmol) of dihydropyran was added. After 48 h of refluxing the same amount was added again (total of 40 mmol). After 72 h of refluxing the reaction mixture was cooled, quenched with 3 mL of acetic anhydride, and submitted to a normal work-up (CH₂Cl₂, Na₂SO₄). The solvents were removed by distillation at atmospheric pressure and the residue chromatographed on 60 g 15% AgNO₃ on silica and eluted with benzene–ether mixtures, to provide firstly 1.306 g (33%) of 286⁹³ and then 550 mg (21%) of 285.⁹³ 285: ¹H NMR 8 1.20–2.53 (m, 4, C₂, C₃ H), 1.97 (s, 3, OCOCH₃), 4.00 (t,
2, J=6 Hz, Cl H), 4.80-6.30 (m, 3, olefinic H). 286:

\[ \text{H NMR: } \delta \ 0.93 (t, 3, J=9 Hz, C7 H), 1.10-2.40 (m, 6, C2, C3, C6 H), 1.93 (s, 3, OCOCH}_3, 3.97 (t, 2, J=6 Hz, Cl H), 5.07-5.70 (m, 2, olefinic CH); \text{C NMR:} \]

Equilibration\(^\text{62}\) of 286, analogously to 273-274, led to a 1.4:1 E-4-hepten-1-yl acetate\(^\text{93} - 286\) ratio by \text{C NMR:}

\[ \text{E-4-hepten-1-yl acetate: } \text{C NMR:} \]

4-Penten-1-yl Acetate, 285, Z-4-Hepten-1-yl Acetate, 286, from 87

To 1.355 g (2.5 mmol) of 87\(^\text{94}\) in 5 mL ether frozen by cooling with liquid nitrogen was added 15 mL (25 mmol) of ethylmagnesium bromide solution (1.66 M in ether) followed by a further 5 mL of ether. This mixture was allowed to warm slowly to room temperature after which ether was distilled and replaced by benzene (25 mL net). Following the addition of 1.84 mL (20 mmol) of dihydropyran, the reaction
mixture was refluxed for 16 h at which point 920 µL (10 mmol) of dihydropyran was added. The same amount more was added after 32 h of refluxing (total of 40 mmol). After 48 h of refluxing the reaction mixture was cooled, quenched with 3 mL of acetic anhydride, and submitted to a normal work-up (CH₂Cl₂, Na₂SO₄). Solvents were removed by distillation at atmospheric pressure and the residue chromatographed on 35 g 15% AgNO₃ on silica (vide supra) to provide 1.935 g (62%) 286 and 325 mg (13%) 285.

2-Phenylnaphthalene, 288, from 2-Methoxynaphthalene, 287

Normal catalyst reduction was carried out with 327 mg (0.5 mmol) of 65 and 0.34 mL (1 mmol) of methylmagnesium bromide solution (2.95 M in ether). Following the addition of 7.2 mL (10.1 mmol) of phenylmagnesium bromide solution (1.4 M in ether), ether was distilled and replaced by benzene (14 mL net). After the addition of 790 mg (5 mmol) 2-methoxynaphthalene, the reaction mixture was refluxed for 14 h, cooled and worked up (petroleum ether, MgSO₄). The solvents were removed to yield a white solid which, when crystallized from methanol, provided 780 mg (76%) of 288.95 One recrystallization from ethanol gave material of m.p. 100-102°C (lit.:95 m.p. 102°C): MS: 204(M⁺,86), 203(25), 202(30), 76(21), 75(27), 74(30), 58(52), 57(23), 52(29), 51(100), 50(84).

2-Phenylnaphthalene, 288, from 2-Naphthol, 289

Normal catalyst reduction and phenol deprotonation
were carried out with 327 mg (0.5 mmol) of 65, 2.40 mL (6 mmol) of methylmagnesium bromide solution (2.5 M in ether), and 720 mg (5 mmol) of 2-naphthol. Following the addition of 4.5 mL (9.9 mmol) of phenylmagnesium bromide solution (2.2 M in ether), ether was distilled and replaced by benzene (12 mL net). After refluxing for 92 h, the reaction mixture was cooled, quenched with aqueous sodium hydroxide solution, and worked up (petroleum ether, MgSO₄). Removal of the solvents and recrystallization of the residue (vide supra) gave 166 mg (16%) 288.
Summary

The reaction of allylic alcohols and Grignard reagents catalyzed by nickel complexes and leading to hydroxy-replaced olefinic products, known as the Felkin reaction, has been shown to be general with respect to structural changes in the Grignard reagent. Specifically, both aromatic and acetylenic Grignard reagents have been demonstrated to participate successfully in the reaction with maintenance of the novel substitution scheme: major products in both instances contained highly substituted allylic carbons. Vinylmagnesium bromide did not behave normally, but instead initiated a disproportionation reaction which was investigated through deuterium labeling experiments. An intramolecular variation of the reaction was demonstrated to occur, although inefficiently. The indolylmagnesium halides have been shown to enter into the Felkin reaction yielding products which in some cases are structurally related to some naturally occurring mold metabolites.

Investigation of structural changes in the allyl alcohol component of the Felkin reaction has revealed that both placing the allyl system within a six-membered ring and attaching substitution at C2 of the allyl alcohol allows the reaction to proceed. Heavy substitution about an allyl alcohol located within a six-membered ring, however, was shown not to yield products of a normal Felkin reaction. The attempted use of an allyl alcohol methoxy-substituted
on the double bond led to the discovery of a new nickel-catalyzed process involving the reaction of enol ethers and Grignard reagents. This reaction yielded olefins derived from substitution of the alkoxy group of the enol ether by the alkyl or aryl group derived from the Grignard reagent. Investigation of several enol ether structural types demonstrated the generality of this process and indicated that the stereochemistry associated with the reaction was mainly retention of enol ether configuration.
References


58. E. Wenkert and E.L. Michelotti, unpublished observations.


