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A DETAILED DESCRIPTION OF THE MECHANISM OF REACTION OF GRIGNARD REAGENTS WITH KETONES.

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Abstract - A detailed description of the reaction of Grignard reagents with ketones is presented based on several studies. The composition of Grignard reagents in Et_2O and THF is described based on molecular association and NMR studies. The cause and mechanisms of formation of pinacol and hydrol in the reaction of "CH_3MgBr" with benzophenone is also described. Several probes to detect the radical nature of the R group in RMgX and the radical anion nature of the ketyl produced in the reduction of the ketone, were used to study the electron transfer nature of Grignard reagent addition to ketones. The results of these studies show clearly that Grignard reagents react with ketones by both a polar and electron transfer pathway. Which of these two pathways involves the lowest energy depends on the nature of the R group of the Grignard, the purity of the magnesium used to prepared the Grignard reagent, the nature of the ketone and the solvent.Grignard reagents that are difficult to oxidize (e.g. 1° R group), ketones that are difficult to reduce (e.g. acetone), solvents of low polarity (e.g., Et_2O) and Grignard reagents made from pure magnesium metal favor a polar pathway, and usually only 1,2-addition product is formed. On the other hand, Grignard reagents that are easily oxidized (e.g. 3° R group), ketones that are easily reduced. (e.g., $Ph_2C{=}O$) solvents of high polarity (e.g., THF, HMPA) and Grignard reagents made from magnesium containing 1st row transition metals, favor an electron transfer pathway. Usually 1,2- and 1,6-addition products are formed as well as some pinacol.

INTRODUCTION

I am, of course, deeply honored to be invited to present our work carried out at Georgia Tech concerning the mechanism of Grignard compound addition to ketones which began in 1964, and which is still in progress (see note a). To have spent so many years studying the mechanism of a single reaction type, I believe, requires some justification. However, in this particular case, I believe such effort is justified in that the reaction of Grignard reagents with ketones is undoubtedly one of the most fundamental reactions in all of organic chemistry, and therefore should be understood in some depth. In addition, whatever has been learned in this study, hopefully can be applied in a broader way to other reactions involving main group organometallic systems, e.g. organolithium and organoaluminum, since detailed mechanistic studies of reactions in main group metal chemistry are rare indeed. We have also made several discoveries of a practical nature during these mechanistic studies which in themselves could easily justify the time and effort spent in this area. The years spent in this work have not been dull since every time we seemed to be coming closer to the end of our study, another major problem in understanding arose which necessitated more effort. There have been a number of times during the past 14 years that the thought of abandoning our efforts crossed our minds as we met what seemed like insurmountable problems. However, because of the unusual experimental skill and determination of my students, who did this work,I am happy to report that we have finally arrived at what we believe to be the beginning of a much better understanding of the mechanism of Grignard reactions.

COMPOSITION OF GRIGNARD REAGENTS IN ETHER SOLVENTS

In order to study the mechanism of Grignard reagent addition to any organic substrate, it is necessary first to understand the nature of Grignard reagents in solution. If Grignard reagents consist of a number of species in soltution, it is also important then to determine which of these species is the most reactive toward the organic substrate being studied. A

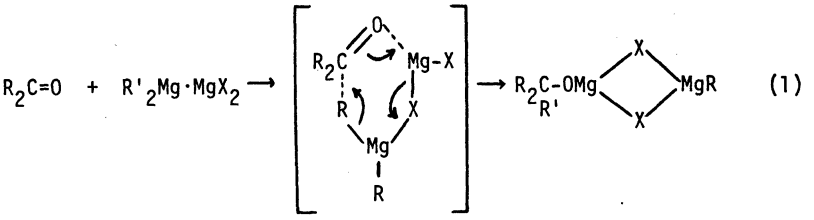
Note a. I would like to dedicate this presentation in honor of a very prominent chemist who has contributed greatly to the field of Grignard chemistry, Professor Henri Normant on the occasion of his 72nd birthday.

study of the prior art in this area of solution composition shows an evolution of thought (Table 1) over the years until 1957 when Dessy presented what appeared to be incontro-

Table 1. Composition of Grignard Reagents in Ether Solvents. A History. (1-6)

YEAR	CONTRIBUTOR	COMPOSITION
1901	Grignard	$RMgX$
1912	Jolibois	$R_2Mg \cdot MgX_2$
1929	Schlenk and Schlenk	$2RMgX \rightleftharpoons R_2Mg + MgX_2$
1957	Dessy	$R_2Mg \cdot MgX_2$
1963	Ashby	$T \rightleftharpoons D \rightleftharpoons 2RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons D \rightleftharpoons T$

vertable evidence (^{28}Mg isotopic labeling experiments) supporting the representation of Grignard reagents by an unsymmetrical dimeric structure ($R_2Mg \cdot MgX_2$). For some years, the unsymmetrical dimeric representation of Grignard reagents received wide acceptance as evidenced by reports from several research groups (7-9) representing the mechanism of Grignard reagent addition to ketones as involving $R_2Mg \cdot MgX_2$ in the transition state (eq. 1).



(1)

In 1963, we questioned the representation of Grignard reagents by a single dimeric structure (5), and we also questioned (6) the non-exchange studies involving Et_2Mg and $^{28}MgBr_2$ which proved (?) the non-existence of RMgX species in solution. Our initial doubt was based on the fact that we and others had shown earlier that R_3Al, R_3B and R_2Hg compounds do exchange readily with their corresponding halides to form R_2AlX, R_2BX and RHgX species and could see no particular reason why R_2Mg compounds would not redistribute with magnesium halides. Initially we were able to show that bromo- and iodo-Grignard reagents are not best represented by a dimeric structure in solution, especially at low concentration.

The following Figures(1-3) display the association curves of various Grignard reagents in ether solvents. Figure 1 shows that typical Grignard reagents (where the halogen is Br or

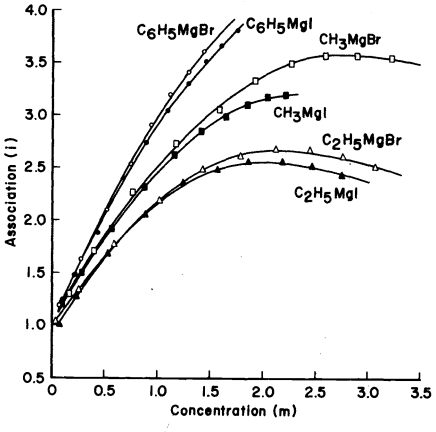


Fig. 1. Association of Alkyl- and Arylmagnesium bromides and iodides in Et_2O.

I), are monomeric at low concentration and associate in a linear polymeric fashion at higher concentrations (10,11). The deviation from a straight line at concentrations > 1m have been shown by equilibrium constant calculations to be due to deviations from ideality at the higher concentrations.

Figure 2 shows that Grignard reagents (where the halogen is chlorine)are predominantly dimeric over a wide concentration range with deviation from ideality greatest for the non-branched reagents (10,11).

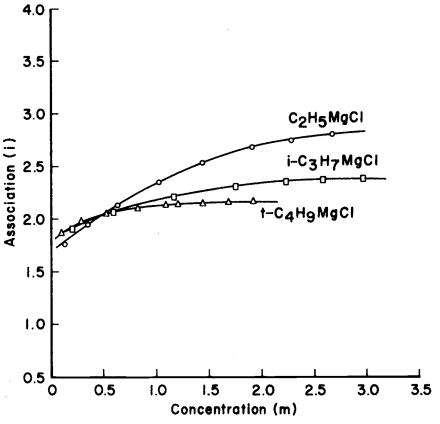


Fig. 2. Association of Alkylmagnesium chlorides in Et_2O

Figure 3 shows that unlike diethyl ether, in THF, RMgX compounds (where X = Cl, Br and R) are monomeric even at high concentration. We did find later that RMgF and RMgOR compounds

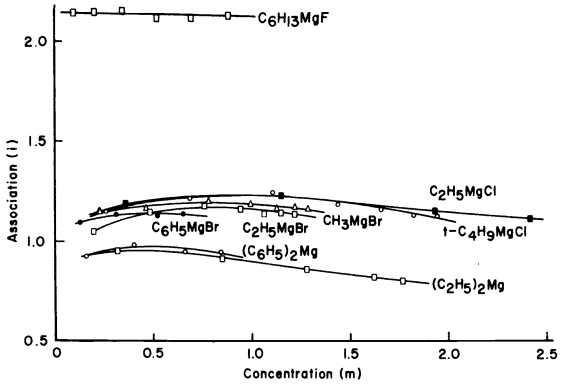


Fig. 3. Association of R_2Mg and RMgX compounds in THF.

are dimeric even in THF due to the stronger bridging characterics of F and OR groups compared to Cl, Br and R. Thus, it is clear that both the solvent and the nature of the X group is important in describing the nature of Grignard compounds in solution.

Although the association data just presented provide valuable information concerning the degree of association of the various species in Grignard solutions, the data say nothing about the identity of the species in solution. Figure 4 shows the results of a variable temperature NMR study of the Grignard reagent prepared from CH_3Br and magnesium metal in diethyl ether (12). The spectra show that although the exchange of methyl groups is fast on the NMR time scale at room temperature such that only one average signal is observed; at temperatures of -100°C., two distinct singlet signals are observed. The lower field signal is assigned to the CH_3MgBr species since addition of $MgBr_2$ to the Grignard solution increased the intensity of this signal relative to the higher field signal. The higher field signal is assigned to $(CH_3)_2Mg$ since it has exactly the same chemical shift as pure $(CH_3)_2Mg$. Thus both the RMgX and R_2Mg species in Grignard reagents have been identified and shown to account for the major species in solution.

The following conclusions, shown in Figure 5, can be drawn from these studies. In diethyl ether, Grignard reagents (where X = Br, I) are best described by the Schlenk equilibrium with monomeric species present at low concentration and linear polymeric association taking

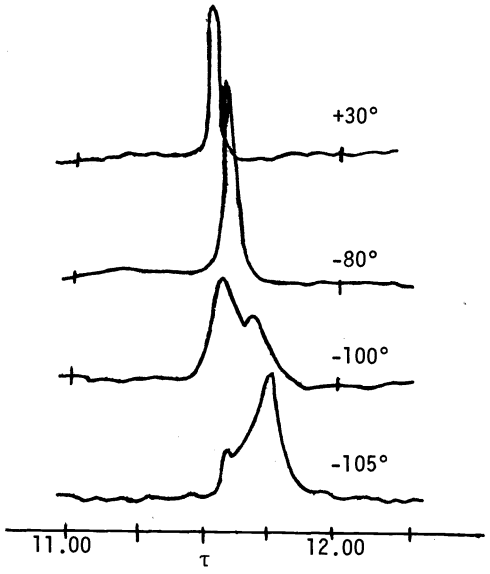
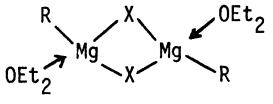


Fig. 4. 100 MHz spectra of CH_3Br Grignard reagent in Et_2O.

Et_2O

$$T \rightleftharpoons D \rightleftharpoons RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons D \rightleftharpoons T$$

X = F, Cl



X = Br, I

THF

X = Cl, Br, I $\quad 2\ RMgX \rightleftharpoons R_2Mg + MgX_2$

X = F, OR

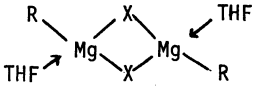


FIG. 5. Composition of Grignard reagents in solution.

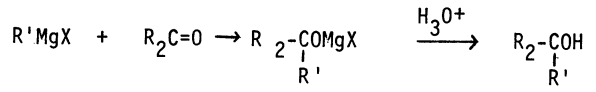
place at higher concentration. However, when X = Cl and F, Grignard reagents are best described by a double halogen bridged dimer at all concentrations. On the other hand, in THF all Grignard reagents, where X = Cl, Br and I as well as R_2Mg and MgX_2 compounds, are monomeric at all concentrations. Only RMgF and RMgOR compounds are dimeric in THF.

The results of the solution composition studies are significant in that they established that both RMgX and R_2Mg species exist in solution and thus both species are capable of reacting with carbonyl compounds. Secondly, it is clear that mechanistic studies involving Grignard reagent addition to organic substrates should be carried out using an "RMgBr"

compound at low concentration in order to avoid the existence of higher associated species in solution which would complicate an already difficult kinetic interpretation.

Table 2 describes the problems associated with the mechanistic interpretation of the reaction of

TABLE 2. Reactions of Grignard reagents with ketones. Major areas of Dispute

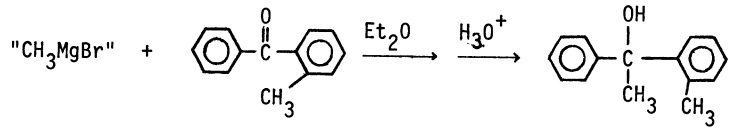


1. Reaction Order of Grignard Reagent
2. Nature of Reactive species (RMgX, R_2Mg, etc.)
3. Origin of By-Product Formation
4. Nature of Alkyl Transfer (Polar or SET Mechanism)

Grignard reagents with ketones. Prior to 1972, the integral order behavior of the organomagnesium reactant had not been determined unequivocally, and it was not known whether RMgX, R_2Mg or some other species was the actual alkylating agent. In the reaction of "CH_3MgBr" with $Ph_2C=O$, both $Ph_2C(H)OH$ and $Ph_2C(H)OHC(H)OHPh_2$ had been observed in significant yield under certain reaction conditions without any evidence for the pathway of formation. Finally, it would be important to determine if the R group from RMgX transfers to the carbonyl carbon atom via an electron transfer (radical) or polar pathway. We believe that we have satisfying answers to all of these questions.

The system that we chose to study is shown in Table 3. In order to determine unequivocally

TABLE 3. Model system selected for kinetic studies.



1. Kinetics determined in excess ketone.
2. Concentration of Grignard < 0.1M.
3. Grignard prepared from single crystal Mg (>99.9995% pure)
4. No enolization or reduction possible
5. Yield of product, 100%.

the integral order behavior of the Grignard reagent, kinetic studies were carried out in excess ketone (13). This kind of study had not been attempted earlier since it was assumed that small differences in Grignard concentration would be difficult to determine; however, it turns out that the change in concentration of the Grignard reagent and ketone with time can be determined accurately by following the disappearance of the uv absorption band due to the complex formed between the Grignard reagent and the ketone.

It was important to keep the Grignard concentration below 0.1m so that associated species would not present a problem in the interpretation of kinetic data. It was also important to prepare the Grignard reagent from unusually pure magnesium metal since we had found that even ppm of certain transition metal impurities in Grignard reagents cause the formation of by-products in significant amounts. The system studied is particularly attractive since enolizaton of the ketone is not possible (no α-hydrogen present in the ketone) and reduction of the ketone is not possible (no β-hydrogen present in the Grignard reagent).

Figure 6 shows that the reaction of "CH_3MgBr" with 2-methylbenzophenone (2-MBP) does not exhibit a simple first order disappearance of Grignard reagent, but that the reaction is more

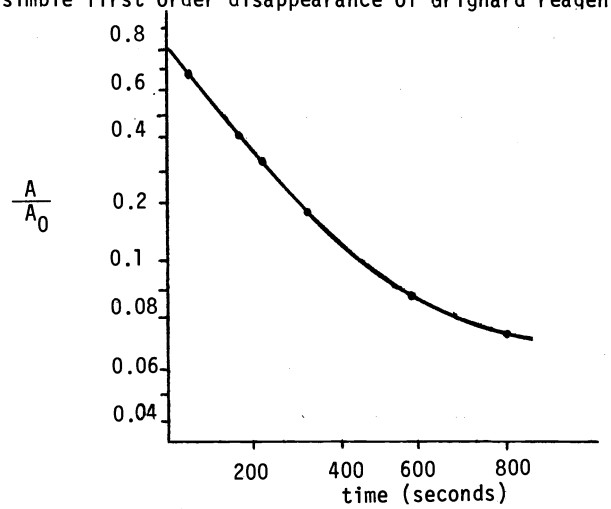


Fig. 6. Reaction of "CH_3MgBr" with 2-MBP in Et_2O.

complex. Therefore,our approach was to carry out a pseudo first-order initial rate study so that we might determine the integral order behavior of the Grignard reagent in the initial stages of the reaction before the complicating features set in.

In this connection, we proposed a model to describe what we thought might be happening in the initial stages of the reaction (Figure 7). In this model, all magnesium species react

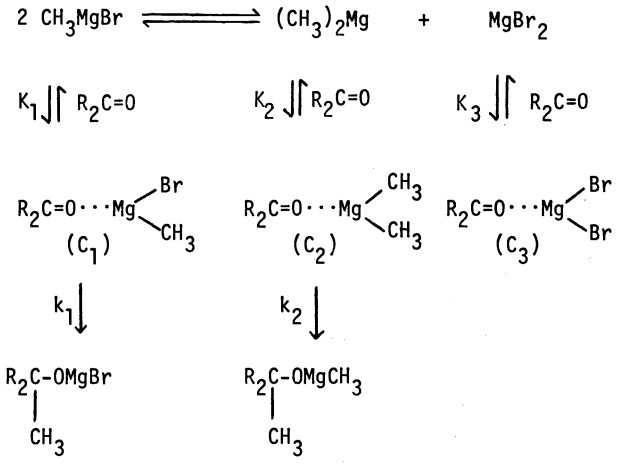


Fig. 7. Model for initial stages of reaction.

rapidly to form a complex with the ketone, the complex then dissociates to form product except in the case of C_3. All of the parameters C_1, C_2, C_3 and K_1, K_2, K_3 and k_2 (14) were determined individually by established methods, and k_1, the rate of reaction of the CH_3MgBr species with 2-MBP, was determined experimentally as shown in Table 4. A differential rate expression (eq. 2) describing the disappearance of C_1 in terms of all of the constants described in eq. 2 was derived for the model system in Fig. 7. The important observation is that for a series of kinetic experiments, the rate constant (k_1) is reasonably constant indicating that the proposed model is correct and that all of the parameters substituted in the differential rate expression are also correct.

$$\frac{d[C_1]}{dt} = \frac{(k_2\sqrt{K_s(1+K_3[K])} + k_1)[K]}{(1 + K_1[K] + 2\sqrt{K_s(1+K_3[K])}} [C_1]_0 \qquad (2)$$

TABLE 4. Determination of k_1. Rate Constants Calculated for Reaction of 0.0124M "CH_3MgBr" with 2-MBP.

$[K]_o$,M	Initial $k_{obs}(sec^{-1})$	$k_1(\ell\ mole^{-1}\ sec^{-1})$
0.128	0.00445	0.0284
0.230	0.00685	0.0253
0.343	0.00879	0.0215
0.448	0.0108	0.0213
0.563	0.0138	0.0245
0.668	0.0149	0.0222
		Ave. 0.0239

In order to test this conclusion further, $MgBr_2$ was added to "CH_3MgBr" in order to shift the Schlenk equilibrium to the RMgX side followed by reaction of this reagent with 2-MBP. In this way, k_1 (rate constant for reaction of CH_3MgBr species with ketone) could be determined directly. Much to our surprise (Figure 8), the first order plot indicating disappearance of

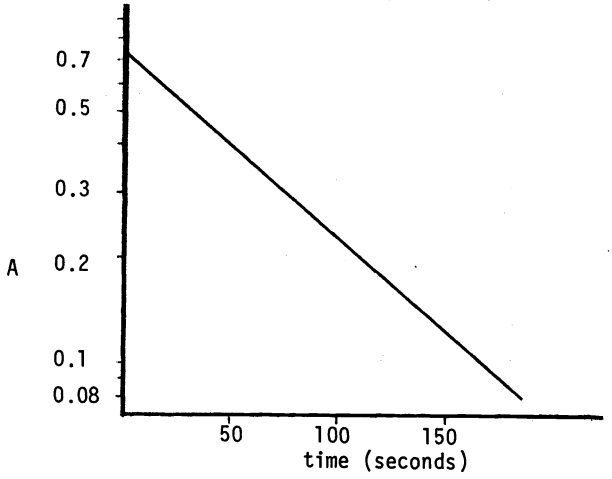


Fig. 8. Pseudo 1st order plot for the reaction of "CH_3MgBr" (with added $MgBr_2$) with 2-MBP.

reagent was linear unlike the result when the Grignard reagent was used without any extra added $MgBr_2$. This result was most fortunate in that it indicates that the reason for the observed curvature in the pseudo 1st order plot involving only the Grignard reagent (no extra added $MgBr_2$) is due to the fact that the Grignard reagent is disappearing in a more complex way (involving the Grignard reagent in the complexity), whereas when excess $MgBr_2$ is added, the $MgBr_2$ serves to eliminate this complication. The suggestion at this point is that the Grignard reagent disappears in a 1st order fashion in its reaction with ketone but it also disappears by complexation with the product to form RMgX·ROMgX; however, when excess $MgBr_2$ is present, the product can complex the stronger Lewis acid ($MgBr_2$) and hence the Grignard reagent disappears in a true 1st order fashion.

In any event, the kinetic results for a series of experiments (Table 5) show not only that k_1 is relatively constant, but that k_1 compares very favorably with k_1 calculated from the differential rate expression described earlier (eq. 2). Thus, from these results, the initial stages of the reaction appear to be as described in the model with the complication of first order kinetic deviation due to reaction of Grignard reagent with product. The latter part of the reaction was studied by adding stoichiometric amounts of preformed product to the Grignard reagent before addition of the ketone. It was possible to show that the Grignard reagent complexes with product in both 1:1 (GP) and 1:2 (GP_2) ratio and that these new complexes then react with the ketone at a slower rate than the pure Grignard reagent (Figure 9). We were able to prepare GP and GP_2 separately and show that the NMR spectra are the same as the spectra exhibited by the species formed in the Grignard reaction in the probe of the NMR spectrometer at -70°C. We were also able to study the rate of

TABLE 5. Reaction of 0.0124 M methylmagensium bromide with 0.462 M 2-methylbenzophenone in the presence of added magensium bromide.

$[MgBr_2]$, M	Initial k_{obsd}, sec^{-1}	Ratio of $MgBr_2$: Grignard	k_1, ℓmol^{-1} sec^{-1}
0.0480	0.00680	4:1	0.0251
0.0240	0.00672	2:1	0.0243
0.0120	0.00672	1:1	0.0239
0.00623	0.00693		Av. 0.0244
0.00268	0.00872		
0.00156	0.00930		
0.000	0.0104		

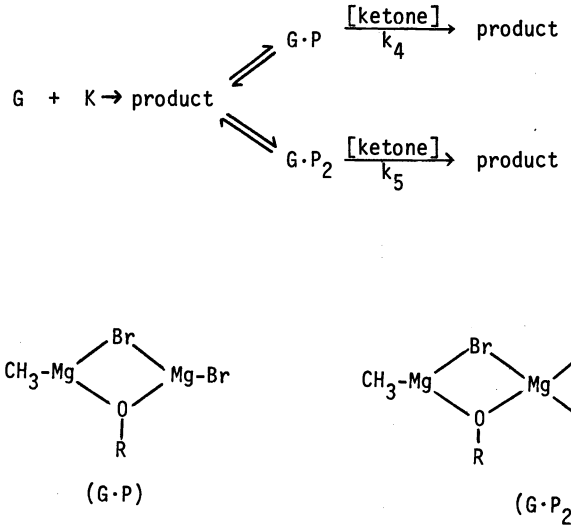
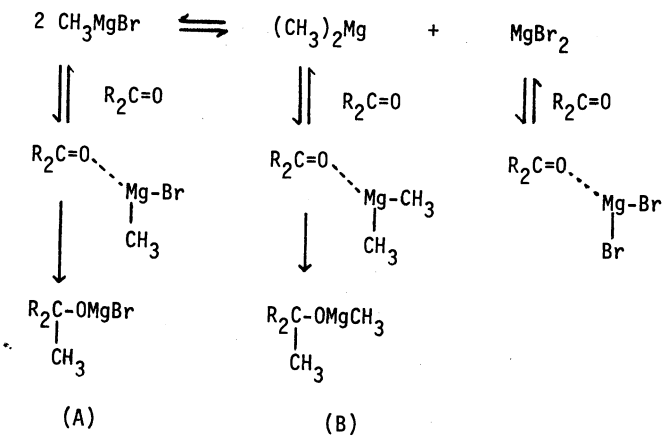
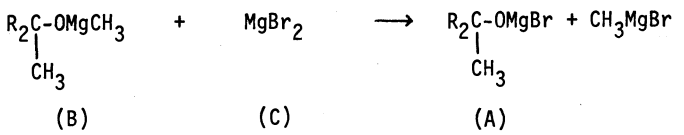


Fig. 9. Latter stages of the reaction of Grignard reagent with ketone.

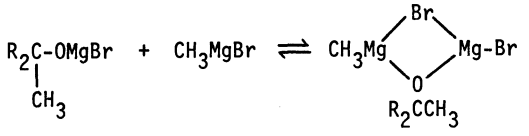
reaction of GP and GP_2 with 2-MBP and show that these are concurrent pseudo 1st order reactions.

Thus it appears clear that the kinetic aspects of the reaction can be described in some detail by the following series of reactions:

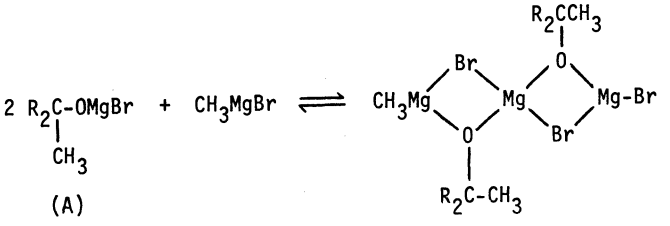




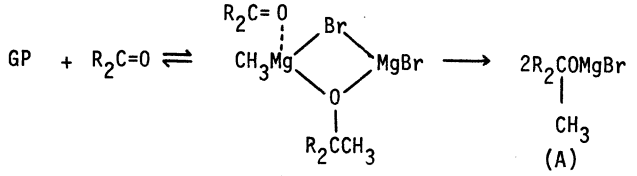
(B) (C) (A)



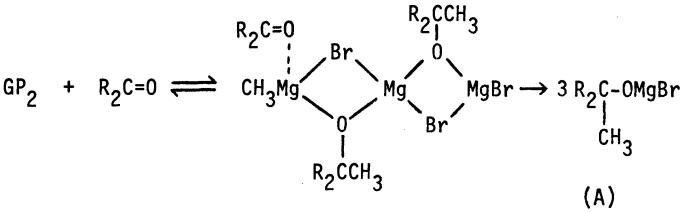
(A) (GP)



(A) (GP_2)



(A)



(A)

This series of equations shows that both the CH_3MgBr and $(CH_3)_2Mg$ species react with the ketone. Although the reaction of $(CH_3)_2Mg$ with ketone in ether is approximately 10 times faster than CH_3MgBr, there is about 10 times more CH_3MgBr than $(CH_3)_2Mg$ in an ether solution of Grignard reagent prepared from methyl bromide and magnesium. Therefore, there is roughly as much reaction taking place via CH_3MgBr as $(CH_3)_2Mg$ species.

Although (B) is capable of reacting further with ketone, we have found that this reaction is relatively slow compared to the reaction of (B) with $MgBr_2$. This latter reaction produces the product plus more Grignard reagent and is very fast on the reaction time scale. Therefore, the formation of (B) cannot account for the observed pseudo 1st order deviation of the reaction. The Grignard reagent then reacts with the product in 1:1 and 1:2 ratio to form GP and GP_2 which then react further with ketone to form more product. The complication of forming GP and GP_2, of course, is observed because the reaction is carried out in excess ketone. When the reaction is carried out in excess Grignard reagent, this complication should not take place since plenty of $MgBr_2$ is available to complex the product without involving RMgX or R_2Mg species.

Two questions were resolved by the kinetic studies just described: (1) the controversy concerning the integral order behavior of the Grignard reagent was settled, i.e. it was shown

unequivocally that the reaction is 1st order in organomagnesium compound and (2) the question concerning the nature of the reactive species was settled, i.e. that reaction in ether proceeds by reaction of both the RMgX and R_2Mg species to about the same extent.

ELECTRON TRANSFER NATURE OF THE REACTION. PINACOL FORMATION.

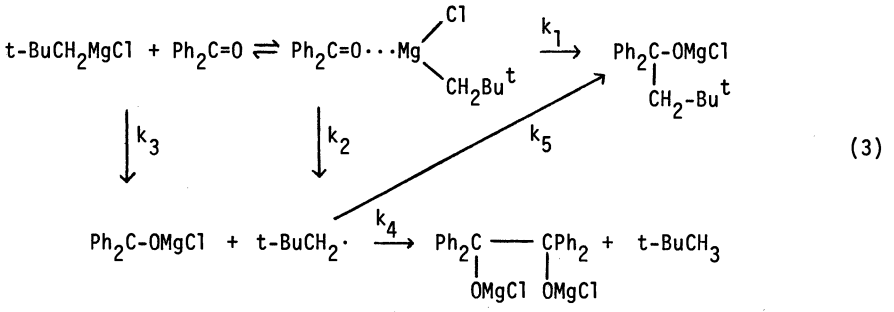
While these questions were being pursued, several reports appeared in the literature begining in 1968, suggesting that the reactions of Grignard reagents with ketones are radical reactions involving electron transfer from the Grignard reagent to the ketone forming a free radical and a ketyl as intermediates. The work of Fauvarque was both early and very important in this connection (15). It was reported (Table 6) that ketyl spectra could be

TABLE 6. ESR observations in the reaction of $(PhCH_2)_2Mg$ (0.375M) with fluorenone (0.345M).

Solvent	%Ketyl
Et_2O	--
THF	>0.1
DME	0.5
Et_3N	>0.2
HMPA	36

observed by e.s.r. spectroscopy when fluorenone was allowed to react with dibenzylmagnesium in various polar solvents. The concentration of ketyl was found to be proportional to the polarity of the solvent with a substantial amount of ketyl (36%) being observed in HMPA. The amount of ketyl observed was also proportional to the particular organomagnesium compound used with electron transfer being observed to a greater degree with those R_2Mg compounds whose R group forms the most stable radical.

Fauvarque suggested a mechanism of organomagnesium compound addition to ketones very similar to that suggested a year later by Blomberg and Mosher(16). The mechanism suggests that 1,2-addition product can be formed not only through a pathway involving a σ complex (k_1),



(3)

but also by a SET pathway (k_5) involving coupling of R· with the ketyl. The ketyl can also couple with itself to form the pinacol and does so in approximately 20% yield. It is significant that neopentane is also formed in 20% yield. The work of Holm (17) with respect to the SET nature of Grignard reactions is most significant. Holm proposed a mechanism in 1971 similar to that proposed by Fauvarque and Blomberg-Mosher and presented strong supporting arguments based on linear free energy studies. His conclusions were broader than previous workers stating that t-butyl Grignard reagents react with aromatic ketones via a SET process and methyl Grignard reagents react via a polar process. Evidence was presented sometime later to support the SET nature of ketone reduction by Grignard reagents.

We were very much aware of these reports appearing between 1968 and 1971 concerning the radical nature of Grignard reactions. We also made some observations during this time that caused us to believe that the reaction was more complicated than the normally depicted polar process. However, at the time, we had all the problems we could handle simply trying to determine the kinetics of the reaction. For example, we found (Fig. 10) that the observed rate constant varied with the initial ketone concentration (upper curve); however, when the Grignard reagent was prepared from single crystal magnesium in excess CH_3Br, there was no

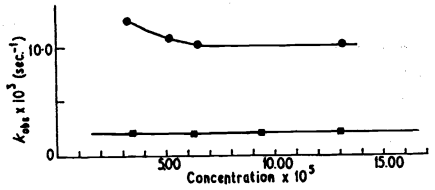


Fig. 10. Effect of initial ketone concentration on rate constants.

no variation and the overall reaction (lower curve) was slower (18). The second observation involved the effect of magnesium metal purity and excess magnesium or CH_3Br in the preparation of the Grignard reagent on the yield of 1,2-addition product (Table 7) (19).

TABLE 7. Product analysis for the Reaction of "CH_3MgBr" with $Ph_2C{=}O$ in Et_2O at 25°C.

Grignard Prepared in excess	$[G]_o/[K]_o$	% Addition	
		Doubly Sublimed Mg	Single Crystal Mg
Mg	57	92	96
"	112	85	95
"	470	73	88
CH_3Br	60	98	98
"	117	97	98
"	487	92	95

It is clear from these data that the ratio of Grignard reagent to ketone, the purity of the magnesium metal used to prepare the Grignard reagent, and whether the Grignard reagent is prepared in excess magnesium or excess CH_3Br, are all important in determining the yield of 1,2-addition product.

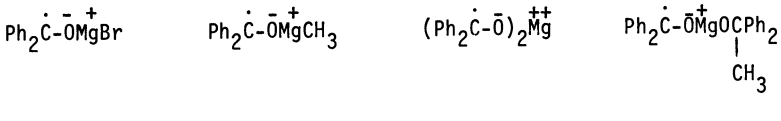
Since the purity of magnesium might possibly be an important factor in the results of Table 7, it was decided to study the effect of pinacol formation in the reaction of "CH_3MgBr" with benzophenone in Et_2O with respect to added transition metal halide (20). All first row transition metal halides were found to be effective in pinacol formation; particularly iron (Table 8). These data show that "CH_3MgBr" addition to benzophenone is very sensitive to transition metal impurities in the magnesium metal whereas "t-Bu-MgCl" reaction with benzophenone is independent of transition metal impurity in the magnesium metal. The suggestion is that the methyl Grignard reagent proceeds predominantly via a polar pathway when the reagent is prepared from pure magnesium; however, a SET pathway can be effected by transition metal catalysis. The data also indicate that the tertiary Grignard reagent is already proceeding by a SET process and therefore addition of catalytic amounts of transition metal halide have little effect on the reaction pathway,including pinacol formation.

If the reaction of "CH_3MgBr" with benzophenone in the presence of added $FeCl_3$ produces

TABLE 8. Comparison of the reaction of benzophenone with Grignard reagents in a 1.5:1 ratio with added $FeCl_3$

Grignard	$FeCl_3$(ppm)	1,2-Addition	1,6-Addition	Pinacol
CH_3MgBr	0	100	--	0
"	40	97	--	3
"	400	81	--	19
"	4000	54	--	46
t-BuMgCl	0	42	48	10
"	400	38	49	12

benzopinacol, it is important to determine if the ketyl is the precursor of the pinacol, and if so, which ketyl is involved. We prepared by unequivocal methods the four possible ketyls (Figure 11) formed in the reaction and compared their esr spectra to the spectrum obtained for



(C) (D) (E) (F)

Fig. 11. Possible ketyls formed in the reaction of "CH_3MgBr" with $Ph_2C{=}O$

the reaction in progress at low temperature in the esr cavity (21). Ketyl (C) was shown to have the same esr spectrum as that observed during the course of the reaction of "CH_3MgBr" and benzophenone in the esr cavity. Furthermore, when the reaction was quenched at any time, the amount of pinacol formed was that calculated based on the absorption of the ketyl as determined by u.v. analysis.

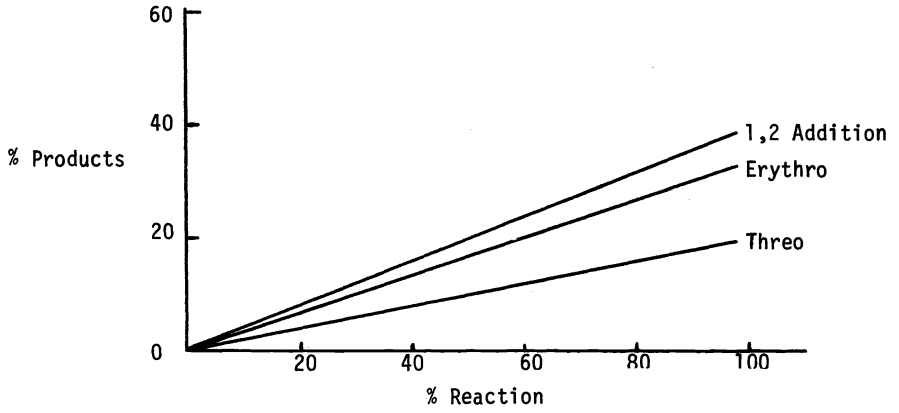
When the reaction of "CH_3MgBr" with 2-MBP in the presence of $FeCl_3$ was allowed to take place at -30°C and then quenched, two pinacols (in nearly equal amounts) were formed, the erythro and threo isomers (20). However, if the reaction mixture was allowed to warm to room temperature, only one isomer was formed. Therefore one pinacol is the kinetic product and the pinacol produced at room temperature is the thermodynamic product. It is interesting to note that the pinacol to 1,2-addition ratio is constant (1.5) throughout the reaction indicating that both reactions proceed via the same intermediate (Table 9). The assignment of the erythro and threo pinacols was based on the rate of oxidation of a mixture of the two pinacols (Figure 12) formed in the reaction at -30°C. These results indicate that the kinetic product is the threo pinacol since the threo pinacol can more easily assume the eclipsed conformation where the OH groups are syn to each other compared to the erythro pinacol where the bulky 2-methylphenyl groups are eclipsed when the OH groups are syn.

Figure 13 shows how the ketyls can combine to form the threo product. The threo product should be the most easily formed (and hence the kinetic product) because of the initial acid-base attraction between magnesium and oxygen. Of course, the threo pinacol can dissociate to the thermodynamically more stable product where the large OMgBr groups are staggared and anti to each other. In time, the ~ 50/50 threo/erythro pinacol equilibrates to a 5/95 mixture at equilibrium.

Single electron transfer to form ketyl is believed to take place via low valent iron (probably Fe^{I}) reduction of the ketone according to the scheme shown (eqs. 4 - 8). The formation of $MeFe^{III}Cl_2$ results in dissociation to $Fe^{II}Cl_2$ which is alkylated followed by dissociation to $Fe^{I}Cl$ which then reduces the ketone to the ketyl. Studies reported earlier indicate that the reducing agent is neither Fe^{III} nor Fe^{II} and that magnesium in some form is attached to the iron reducing agent.

TABLE 9. Reaction of "CH_3MgBr" (0.20M) with 2-MBP (0.02M) in Et_2O at -30° in the presence of $FeCl_3$

Time(min.)	Recovered Ketone(%)	1,2-Addn(%)	Pinacol(%) Erythro	Pinacol(%) Threo	Pinacol/addition
40	82	7	7	4	1.5
120	47	21	19	13	1.5
210	24	31	28	17	1.5



Reactant		Product
45% Kinetic Pinacol	$Pb(OAc)_4$	34% Kinetic Pinacol
+	3 days →	+
55% Thermodynamic Pinacol		55% Thermodynamic Pinacol
		+
		11% Ketone

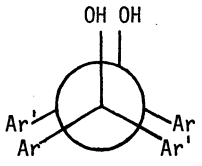


Fig. 12. Determination of the structure of the pinacols.

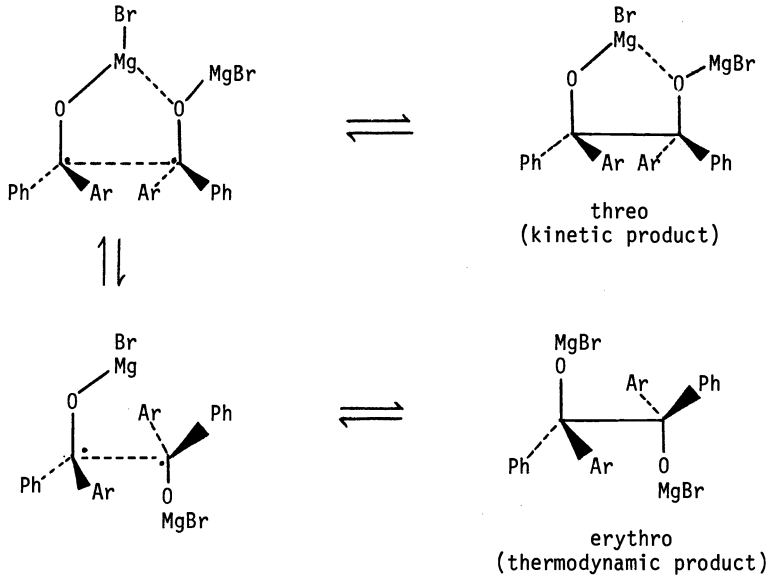


Fig. 13. Formation of kinetic and thermodynamic pinacols.

$$MeMgBr + Fe^{III}Cl_3 \longrightarrow MeFe^{III}Cl_2 + MgBrCl \quad (4)$$

$$MeFe^{III}Cl_2 \longrightarrow CH_4 + C_2H_6 + Fe^{II}Cl_2 \quad (5)$$

$$MeMgBr + Fe^{II}Cl_2 \longrightarrow CH_4 + C_2H_6 + MeFe^{II}Cl + MgBrCl \quad (6)$$

$$MeFe^{II}Cl \longrightarrow CH_4 + C_2H_6 + Fe^{I}Cl \quad (7)$$

$$Fe^{I}Cl + Ph_2C{=}O \longrightarrow Ph_2\dot{C}\text{-}\bar{O}Fe^{II}Cl \xrightarrow{MeMgBr} Ph_2\dot{C}\text{-}\bar{O}\overset{+}{M}gBr + MeFe^{II}Cl \quad (8)$$

HYDROL FORMATION

Having a reasonable understanding of the mechanism of pinacol formation, we shifted our attention toward the formation of another by-product in the reaction of "CH_3MgBr" with 2-MBP, i.e. 2-methylbenzhydrol. We found (Table 10) that at high Grignard:ketone ratios (800:1), a substantial amount (56%) of 2-methylbenzhydrol was formed (22). The formation of 2-methylbenzhydrol in this reaction is highly unexpected since no β-hydrogen exists on the alkyl group of the Grignard reagent in order to effect a β-hydrogen reduction. Since the amount of 2-methylbenzhydrol increases as the G/K ratio increases, one might assume that some impurity in the Grignard reagent is causing this reduction. It also is clear that although the impurity exists in low concentration (~ 0.2%) this impurity can be substantial when the G/K ratio is 800:1, and a substantial amount of benzhydrol can be produced.

When the reaction of "CH_3MgBr" with 2-MBP was carried out in ether at -30°, it was shown that benzhydrol is formed quickly and early in the reaction, even more rapidly than the 1,2-addition product and that the formation of hydrol is essentially complete before much 1,2-addition product is formed (20). This result is expressed in Table 11 and also Figure 14. It was thought initially that possibly some transition metal impurity was causing the formation of hydrol just like iron and other first row transition metals caused the formation of pinacol. However, doping experiments showed that no 1st, 2nd or 3rd row transition metals caused the formation of 2-methylbenzhydrol when the reactants were allowed to react in 1:1 ratio (20). We were further concerned that possibly the intermedidate ketyl, in the presence of a large excess of Grignard reagent, was abstracting hydrogen from solvent, or even possibly a dianion was formed which abstracted a proton from solvent to form the

TABLE 10. Effect of Grignard:ketone ratio on products from the reaction of "CH_3MgBr" with 2-MBP in ether at room temperature.

[MeMgBr] moles/ℓ	[2-MBP] moles/ℓ	G/K	%YIELD 1,2-Addn'	Pinacol	2-methylbenzhydrol
0.010	0.99	1:100	100	0	0
0.010	0.11	1:10	100	0	0
1.50	1.50	1:1	100	0	0
1.50	0.15	10:1	99	0.6	0.4
1.50	0.015	100:1	89	2	9
1.50	0.00375	400:1	62	2	36
1.50	0.001875	800:1	40	4	56

TABLE 11. Reaction of "CH_3MgBr with 2-MBP in Et_2O at -30°C.

Time(hrs.)	Unreacted ketone(%)	(%) 1,2-addition	(%) 2-methylbenzhydrol	(%) Pinacol	By-Product :addition
0.2	68	2.7	28	1.7	10.8
1	46	18	34	2.0	2.0
4	11	48	39	2.3	0.85
12	0	56	41	2.5	0.77

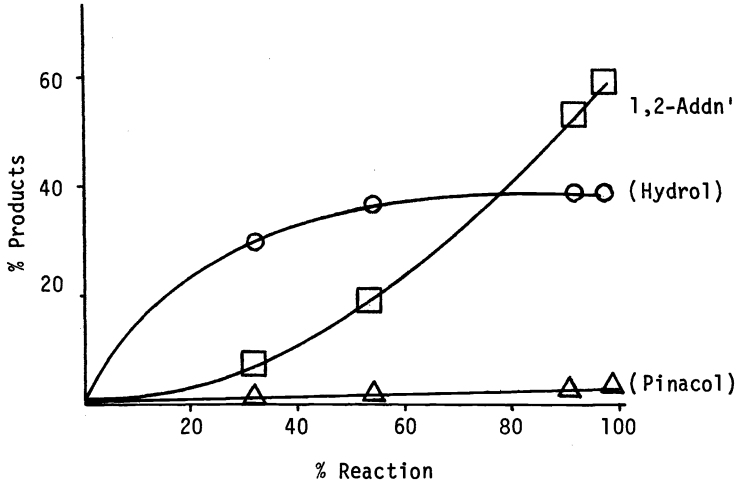
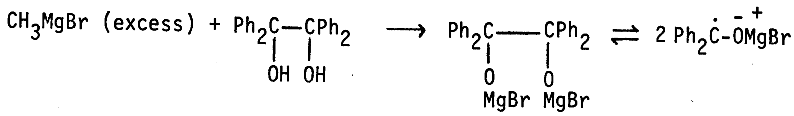


Fig. 14. Graphical representation of data in Table 11.

hydrol. However, the ketyl of 2-MBP was prepared by adding a large excess of "CH_3MgBr" to the pinacol and the ketyl allowed to stand for 2 days (eqs. 9-10). When the reaction mixture was hydrolyzed,only the pinacol was regenerated.

The above results indicated the necessity of determining the origin of the hydrogen that is reducing the ketone to the hydrol. We carried out a series of experiments (Table 12) that indicate that the hydrogen that reduces the ketone comes from the solvent and that the



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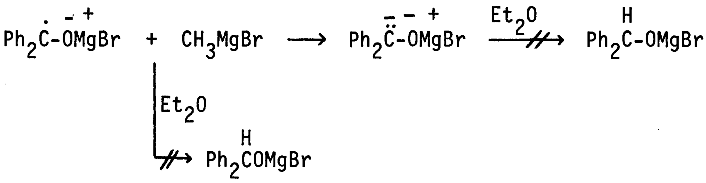

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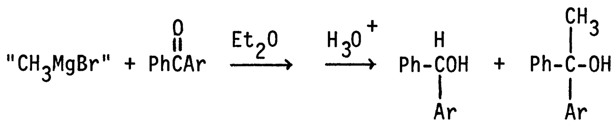
TABLE 12. Origin of hydrogen involved in the formation of hydrol from ketone.



Grignard Formed in	Reaction Carried out in	Ph-C(H)(OH)-Ar	Ph-C(D)(OH)-Ar
$CH_3CH_2OCH_2CH_3$	$CH_3CH_2OCH_2CH_3$	59	--
$CH_3CD_2OCD_2CH_3$	$CH_3CD_2OCD_2CH_3$	0	27
$CH_3CH_2OCH_2CH_3$	$CH_3CD_2OCD_2CH_3$	65	0

reducing species is formed in the Grignard preparation and not during the reaction with ketone (22). The first two experiments show that the hydrogen involved in reduction of the ketone comes from the solvent and since it is the α-D that is abstracted, the hydrogen atom is abstracted by a radical. The low (27%) yield of the deuterium compound is a result of a primary deuterium kinetic isotope effect. The final experiment in which the Grignard reagent is prepared in protio diethyl ether and then the solvent replaced by the α-deuterio ether before reaction with ketone, shows that only the protio reduction product is formed. This result indicates that the hydride reagent that reduces the ketone is formed during the Grignard formation step. Since the magnesium used in these experiments is at least 99.99% pure, the immediate suggestion is that MgH_2 is formed as a result of radical abstraction of hydrogen from solvent during the Grignard preparation (Figure 14).

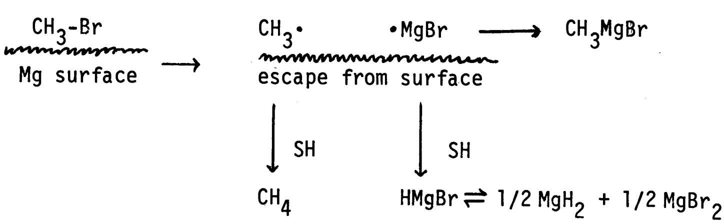


Fig. 14 Formation of Mg-H species in Grignard formation.

Considerable evidence to establish this point was accumulated by doping Grignard reagent with MgH_2 (prepared independently) and showing that reduction takes place readily to give the same yield and stereochemistry with several ketones as was obtained from a Grignard reagent that produced reduction product without being doped with MgH_2.

An interesting point here is that some Grignard reagent preparations gave substantial amounts of reduction product and others did not. We could not relate this difference to purity of magnesium metal, but did relate it to the particle size of the magnesium used in the Grignard preparation. The data reported in Table 13 show that when the magnesium

TABLE 13. Importance of magnesium shaving size in the preparation of "CH_3MgBr" prior to reaction with 2-MBP at 400:1 ratio in Et_2O

Mg Shaving Size	CH_3MgBr Flow Rate(cc/min)	% Yield	
		1,2-Addition	Hydrol
Fine	214	41	59
Fine	682	74	27
Medium	682	84	16
Large	682	91	9

particle size is small, reaction of magnesium metal with CH_3Br takes place rapidly and the MgH_2 formed can reduce ketone to hydrol. However, as the CH_3Br addition rate is increased and the magnesium metal particle size increased, the amount of excess CH_3Br at any time is large and when the MgH_2 by-product is formed, it reacts with the excess CH_3Br. Thus, the amount of hydrol produced in every case was a function of the size of the magnesium shavings rather than magnesium purity. When an experiment was carried out using fine magnesium shavings at a CH_3Br addition of 214 cc/min and then excess CH_3Br added after the Grignard preparation was complete,followed by ketone addition, only 3% hydrol was formed.

The Nature of Alkyl Transfer from the Grignard Reagent to the Carbonyl Carbon Atom

The final problem to be discussed involves the question of the exact manner in which the R group from the Grignard reagent attacks the carbonyl carbon atom. Previous workers (14-16) have suggested a mechanism shown earlier and slightly expanded upon here (Fig. 15). It is

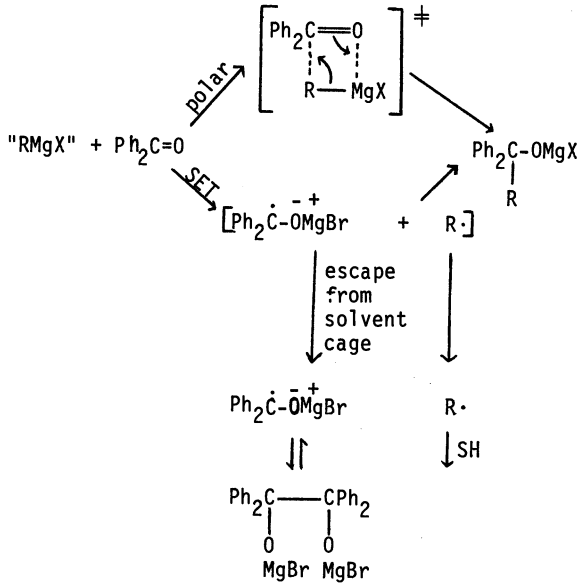


Fig. 15. Suggested mechanism of Grignard reagent addition to ketones

suggested that 1,2-addition product can be formed either by a polar or SET mechanistic pathway. If 1,2-addition product is actually formed via a SET pathway, then evidence might be obtained for the intermediacy of the free radical and the radical anion. In this connection, probes could be used to detect both the free radical and the ketyl, provided that the rate of coupling of the radical and ketyl to form 1,2-addition product does not greatly exceed the rate by which the probes isomerize, cyclize, etc. For this reason, we have used a number of probes to test the intermediacy of the ketyl and the radical. We shall discuss first ketyl probes.

The first ketyl probe used (23) is a cis enone that has the ability to isomerize to the trans enone, if indeed it is reduced to a ketyl (Figure 17). If the cis-enone is reduced to

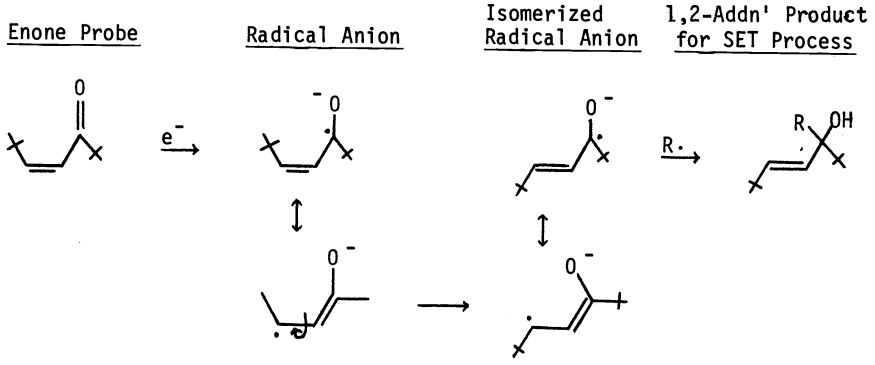


Fig. 16. Detection of a ketyl intermediate using a cis enone.

TABLE 14. Results of enone probe.

Grignard Reagent	Recovered Enone (%)cis	(%)trans	1,4-Addition(%)	1,2-addition(%) trans	cis	1,2-Reduction(%)
t-BuMgCl	4	96	12	25	3	60
MeMgBr	83	17	41	40	19	0
AllylMgBr	99	1	0	1	99	0

the ketyl, it will rapidly isomerize to the trans ketyl which on coupling with R· will produce the trans-1,2-addition product. Experiments (Table 14) were carried out such that the enone was used in 100% excess so that unreacted enone could be recovered. The data show that when t-BuMgCl was allowed to react with 100% molar excess of cis enone, most (96%) of the recovered enone isomerized to the trans enone and most of the 1,2-addition product also exhibited trans stereochemistry. Hence, it appears that the predominant pathway for the reaction of a 3° Grignard reagent, even with a ketone that is less easily reduced than benzophenone, is an electron transfer pathway producing a ketyl as an intermediate. The results with MeMgBr, however, are not so straightforward. In this case, not nearly as extensive isomerization has taken place either in the recovered enone probe or in the 1,2-addition product. The conclusion is that either there are two competing reaction pathways (polar and SET or that coupling of the ketyl and free radical are somewhat faster than the rate of isomerization. The allyl Grignard presents a very interesting case in that no isomerization was observed either in the enone probe recovered or the 1,2-addition product. Since the allyl Grignard would be expected to reduce the enone faster than the other Grignard reagents and the resulting allyl radical should be more stable than either Me· or t-Bu· toward further reaction, one should have observed significant isomerization if a SET process was in effect. It would appear that this reaction may proceed by a polar process since the allyl carbanion is also more stable than Me^- or $t\text{-}Bu^-$ carbanion and should effect 1,2-addition via a polar process more easily than MeMgBr or t-BuMgCl.

Another ketyl probe involves the trapping of the ketyl and thus short circuiting the

formation of 1,2-addition product (24). Kornblum has shown that p-dinitrobenzene, which is more easily reduced, will capture an electron from a radical anion whose conjugate ketone has a higher reduction potential (25). Consequently, we have added p-DNB to a mixture of Grignard reagent and ketone in order to trap any ketyl formed in the reaction and thus prevent the formation of 1,2-addition product (eqs. 11 and 12). The results of these experiments (eqs. 13 and 14) show that both "CH_3MgBr" and "t-BuMgCl"

$$\text{"RMgX"} + Ph_2C{=}O \xrightarrow{SET} Ph_2\dot{C}\text{-}O^{-}Mg^{+}Br + R\cdot \longrightarrow \underset{R}{Ph_2C}\text{-}OMgBr \qquad (11)$$

$$\text{p-DNB} + Ph_2\dot{C}\text{-}O^{-}Mg^{+}Br \longrightarrow Ph_2C{=}O + [\text{p-DNB}]^{\dot{-}}\,Mg^{+}Br \qquad (12)$$

$$\text{"}CH_3MgBr\text{"} + Ph_2C{=}O + \text{(p-dinitrobenzene)} \longrightarrow \begin{array}{l}(1)\ \text{Rate of 1,2-addition not affected}\\(2)\ \text{Pinacol formation completely inhibited}\end{array} \qquad (13)$$

$$\text{"t-BuMgCl"} + Ph_2C{=}O + \text{(p-dinitrobenzene)} \longrightarrow \text{(same)} \qquad (14)$$

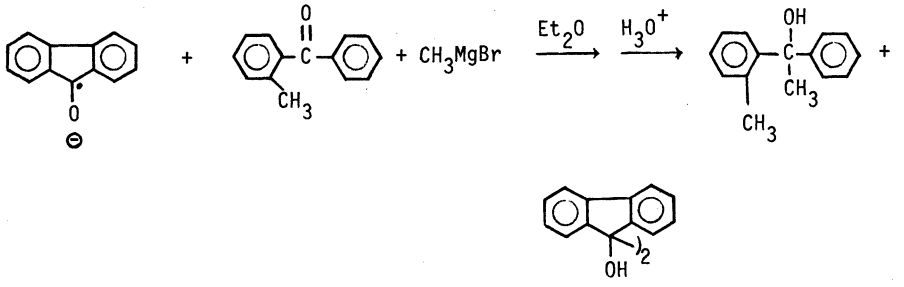
react with $Ph_2C{=}O$ at the same rate in the presence or absence of p-DNB, but that pinacol formation is completely inhibited. It is clear then that p-DNB will indeed capture the radical anion if it is free and there is sufficient time for reaction of the p-DNB with the radical anion. However, the fact that the formation of 1,2-addition product is not affected by p-DNB indicates either that the ketyl is not free and is bound as a tight radical pair with a radical cation ($[RMgX]^{\dot{+}}$) and hence cannot be trapped by the p-DNB before it reacts to form 1,2-addition product or that the ketyl is free but simply reacts much too fast with the alkyl radical ($R\cdot$) to be trapped by the p-DNB.

A further probe into the reality of a ketyl intermediate was made by use of a ketyl crossover experiment (26). The crossover experiment is based on the premise that if a ketyl and a free radical are generated during the reaction, the addition of another ketyl of appropriate reduction potential will cause the formation of 1,2-addition product corresponding to the added ketyl in addition to the expected product (eq. 15). In order to test this hypothesis, 2-methylbenzophenone and fluorenone ketyl were allowed to react independently with "CH_3MgBr" and "t-BuMgCl" (eqs. 16 and 17). In each case, it was shown that no 2-methyl-

$$R_2C{=}O + R'MgX \longrightarrow R_2\dot{C}\text{-}O^{-}Mg^{+}X + R'\cdot \xrightarrow{k=10^8} \underset{R'}{R_2C}\text{-}OMgX$$
$$\Big\downarrow\Big\uparrow\ R''_2\dot{C}\text{-}O^{-}Mg^{+}X$$
$$\underset{R'}{R''_2C}\text{-}OMgX \qquad (15)$$

benzophenone was recovered and that the 2-MBP ketyl did not admix with the fluorenone ketyl; otherwise, the fluorenone ketyl would also have been coupled by the free radical to form 1,2-addition product.

It appears then that the ketyl probes cited here have given some evidence of the formation of ketyls, but that these ketyls react rapidly with the free radical compared to the probe. The result is that the probes are not entirely effective in the unequivocal establishment of the integrity of the ketyl as the precursor to 1,2-addition product. Of course,



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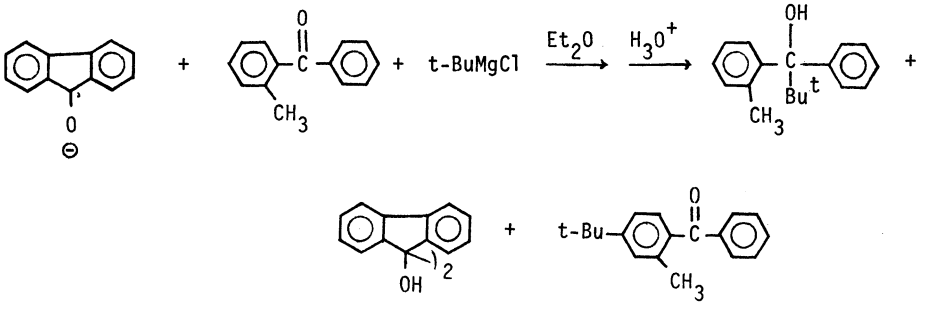

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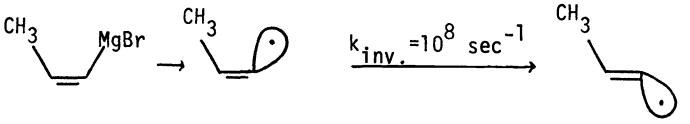
detection of free radicals would be indirect evidence to support the intermediacy of ketyls since the ketyl and radical are formed as co-products.

Evidence for Radical Intermediates

We have investigated several systems as probes for radical intermediates. We prepared cis-propenylmagnesium bromide for reaction with benzophenone (eq. 18 and 19) so that if a free



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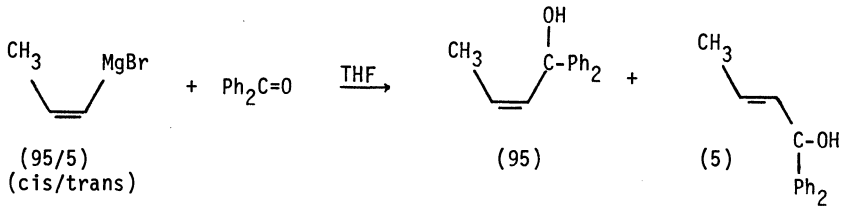
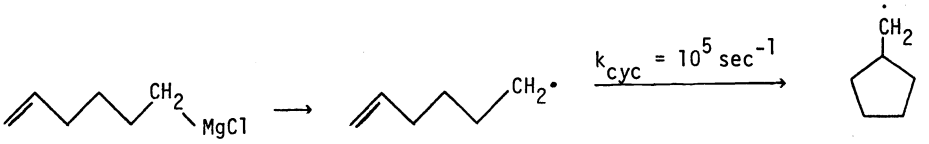
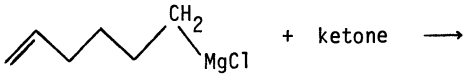


(19)

radical is formed in the reaction, isomerization to the trans propenyl radical would take place (27). Detection of such an event takes place by characterization of the 1,2-addition product and determining whether the added group is a cis or trans propenyl group. In the present case, there was no detection of an isomerized product. Either the free radical was not formed or it coupled so fast with the ketyl that isomerization was not possible on the reaction time scale. In the latter case, the rate constant of the coupling reaction would have to be about 10^{10}-10^{11} sec^{-1}.

Another probe investigated involves the cyclization of an alkyl radical containing a terminal double bond (Figure 17) (27). It is known that the hexenyl radical cyclizes at the rate, $k = 1 \times 10^5$ sec^{-1} (28); therefore, if such a radical is formed in the reaction of hexenyl Grignard reagents with ketones, cyclized 1,2-addition product should be observed. When such a reaction was carried out with 5-hexenylmagnesium chloride and benzophenone in





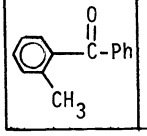
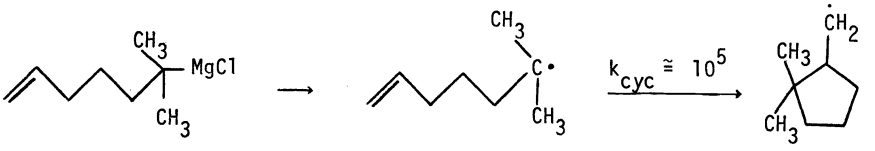
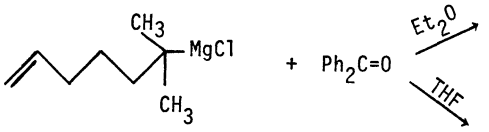
KETONE	SOLVENT	(%) 1,2-ADDITION	(%) HYDROL
$Ph_2C=O$	Et_2O	51 (uncyc.)	49
	THF	28 (uncyc.)	72

Fig. 17. 5-Hexenylmagnesium chloride as a free radical probe





1,2-ADDN'(%)	1,6-ADDN'(%)
39 (0% cyc)	61 (73% cyc)
58 (41% cyc)	42 (81% cyc)

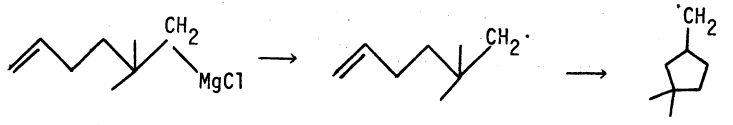
Fig. 18. 1,1-Dimethyl-5-hexenylmagnesium chloride as a free radical probe.

Et_2O or with 2-MBP in THF, no cyclized 1,2-addition product was observed. The conclusion once again is either that SET does not take place to produce a free radical or if the radical is formed it couples with the ketyl more rapidly than it can cyclize.

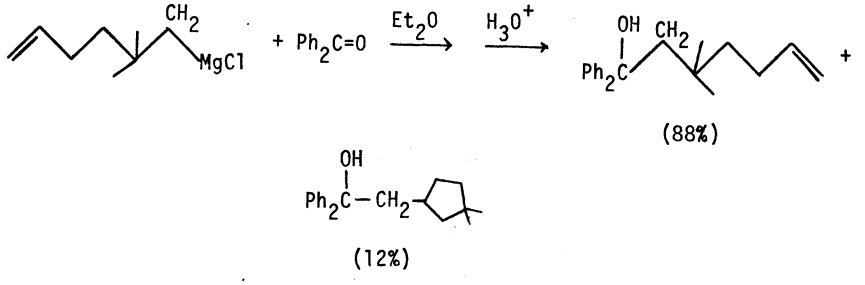
In order to test the concept of free radical cyclization in Grignard-ketone reactions, we allowed a tertiary Grignard probe to react with benzophenone (Figure 18). The results show that although no cyclization of the 1,2-addition product is observed in the reaction of the 3° Grignard probe with $Ph_2C=O$ in Et_2O, in THF the 1,2-addition product is 41% cyclized. This is the most direct evidence that 3° Grignard reagents form 1,2-addition product by an electron transfer process producing a free radical as an intermediate (17). In both Et_2O and THF, the 1,6-addition product was found to be substantially cyclized indicating a breakage of the C-Mg bond to form 1,6-addition product. However, in Et_2O, the C-Mg bond may stay intact in forming 1,2-addition product since non cyclization of the probe was observed and yet the rates of formation of 1,2- and 1,6-addition product were comparable.

The indications are that the rate determining step in 1,2-addition is electron transfer followed by a very rapid coupling of the radical or incipient radical with ketyl to form product. Cyclization of R, when R = 3° radical, takes place because the rate of 3° radical coupling with ketyl is slower than primary radical coupling due to the greater stability of the 3°

radical. In addition, cyclized 1,2-addition product was observed in THF (and not in Et_2O); a solvent that should stabilize the ketyl. If this premise is correct, then we might be able to observe cyclization of a 1° Grignard probe, if indeed a free radical is formed, by simply slowing down the very fast coupling step so that the 1° Grignard probe would have time to cyclize. In this conncection, we prepared neooctenylmagnesium chloride and allowed it to react with $Ph_2C{=}O$ in Et_2O (eqs. 20 and 21). In this case, only 1,2-addition product



(20)



(88%)

(21)

was formed, 12% of which was cyclized (26). This is the first definitive evidence showing that even 1° Grignard reagents react with $Ph_2C{=}O$ at least to some extent by SET. When a similar reaction was carried out with 2-MBP in ether, no cyclized 1,2-addition product was formed; however, 14% 1,6-addition product was formed which was 68% cyclized. This is the first reported case of a 1° Grignard reagent giving 1,6-addition product.

The last and possibly strongest evidence showing the broad relationship between polar and SET reactions with respect to the nature of the Grignard and ketone studied comes from a relative rate study (Table 15) (29). These results show that with a ketone that is diffi-

TABLE 15. Relative rates of reactions of Grignard reagents with ketones.

R(in RMgX)	$CH_3-\overset{O}{\overset{\|}{C}}-CH_3$	$Ph-\overset{O}{\overset{\|}{C}}-Ph$
CH_3-	1,114	30
C_2H_5-	2,324	408
$CH_3-\overset{H}{\overset{\|}{C}}-\overset{\|}{CH_3}$	272	4,027
$CH_3-\overset{CH_3}{\overset{\|}{C}}-\overset{\|}{CH_3}$	9	5,363

cult to reduce (such as acetone), the order of Grignard reaction rates is Me > Et > i-Pr > t-Bu as would be expected for a polar reaction. However, when the ketone is so easily reduced that electron transfer (as in the case of aromatic ketones) can take place the order is just the opposite, i.e. t-Bu > i-Pr > Et > Me. It is demonstrated

that the mechanistic pathway (polar or SET) depends both on the nature of the ketone (reduction potential), the nature of the Grignard reagent (oxidation potential) and probably to some extent, the nature of the solvent and the nature of the halogen. Thus, SET is favored by 3° over 1° Grignard reagents, ketones more easily reduced over those more difficultly reduced and by highly polar solvents. Still to be studied thoroughly is the effect of halogen in RMgX on electron transfer.

It appears then that a rather general picture can be drawn to represent the transition state involving alkyl group transfer in the reaction of 1°, 2° and 3° Grignard reagents with aromatic ketones. In this transition state, electron transfer has already taken place in the prior step such that partial radical character exists at the R group of the Grignard, the

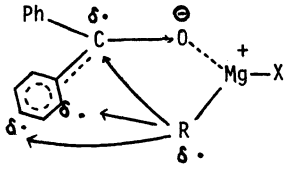
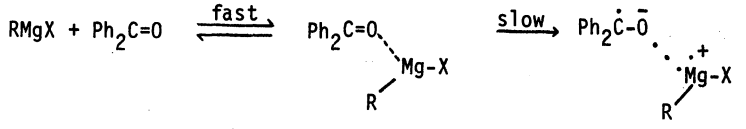


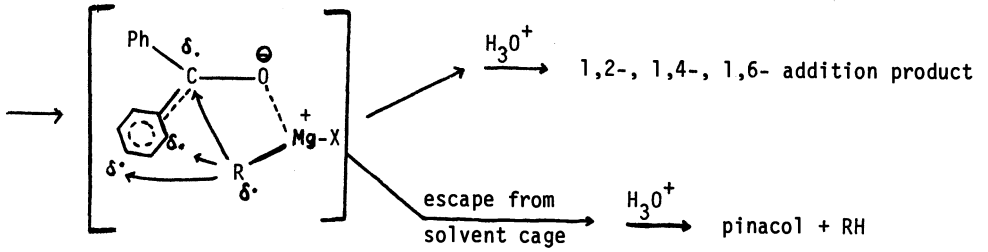
Fig. 19. Transition state depicting alkyl group transfer

carbonyl carbon and the 2 and 4 positions of the phenyl group. When the R group is 1°, such as methyl, the CH_3·radical (if formed) is short lived because it is so reactive. Primary Grignard reagents give exclusively 1,2-addition product and have not had time to cyclize or isomerize before coupling with the carbonyl carbon. If, however, the rate of coupling can be slowed down such as in the case of the 1° neooctenyl Grignard probe, then the radical has time to cyclize and even add to the 4-position of the phenyl ring to give 1,6-addition product. In the case of 3° Grignard reagents, the dissociation of the R-Mg bond takes place more readily due to the stability of the incipient 3° alkyl radical. When the radical is formed, it has sufficient stability that it can cyclize and add to any of the available radical positions. In the case of 1° Grignard reagents, it is easy to see that there is also the possibility that a "free" radical is not formed or if it is, it couples so quickly with the carbonyl carbon as to be undetectable. Such a process would be difficult if not impossible to distinguish from a polar process.

We can now write a mechanism which fits all of the data obtained so far (eqs. 22 and 23).



(22)



(23)

The first step is a diffusion controlled acid-base reaction forming a σ-complex. The next step involves electron transfer which is the rate determining step of the reaction. R· coupling of the three positions possessing radical character produces 1,2-, 1,4-, and 1,6-addition product whereas escape of the radical anion and radical cation from the solvent cage results in R· abstraction of hydrogen from solvent and dimerization of the radical anion to form the magnesium salt of the pinacol.

The overall scheme depiciting all of the different reaction pathways in which a Grignard reagent can react with a ketone is shown in Figure 22. In this presentation, we and others

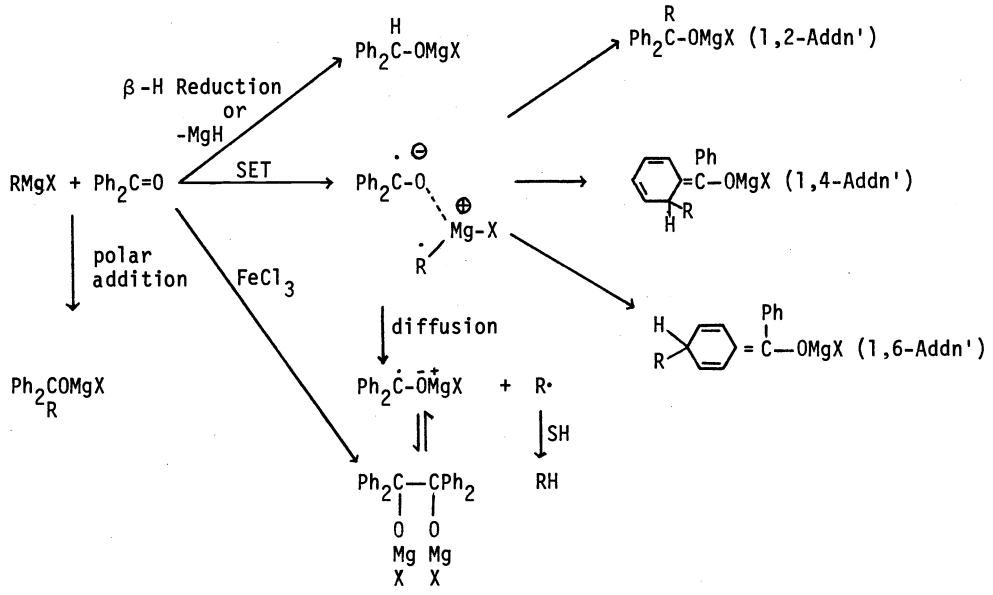


Fig. 20. Pathways involved in the reaction of Grignard reagents with ketones

have considered and established the integrity of each individual pathway. The electron transfer pathway is a recently established pathway compared to the other pathways and has shed some light on the overall understanding of this important reaction. It is not only conceivable, but probable that a better understanding of such an important reaction will lead to even more important discoveries involving the use of Grignard reagents in the future.

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