Organometallic Reaction Mechanisms. 15. Factors Influencing the Nature of Grignard Reactions with Ketones

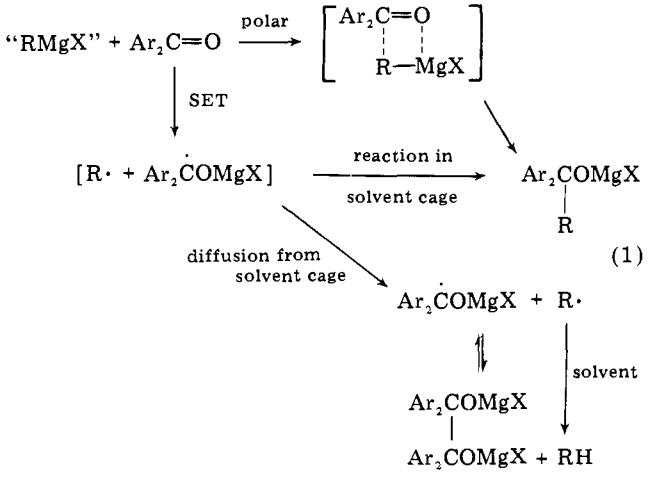
E. C. Ashby* and T. L. Wiesemann

Contribution from the School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332. *Received May 16, 1977*

Abstract: The reactions of benzophenone and fluorenone with *tert*-butylmagnesium chloride and methylmagnesium bromide were studied under a variety of conditions. The methyl Grignard reactions were dramtically affected by transition metal impurities in the magnesium used to prepare the reagent; however, the *tert*-butyl Grignard reactions were unaffected by transition metal content. When single electron transfer occurred, it was enhanced by an increase in solvent polarity. An iron(I) intermediate is proposed to be the active species leading to iron catalyzed pinacol formation in methyl Grignard reactions with aromatic ketones. The reactions of acetone with methyl and *tert*-butyl Grignard reagents were also studied. While methyl Grignard reactions were unaffected by changes in reaction conditions, the addition of $FeCl_3$ to the reaction of *tert*-butylmagnesium chloride with acetone leads to a high yield of reduction product. An iron hydride intermediate was proposed to account for this observation. The presence of *p*-dinitrobenzene in Grignard reactions with 2-methylbenzophenone was shown to inhibit pinacol formation, but to have no effect on the ratio of 1,2:1,6-alkylation. A general mechanism for the reaction of Grignard reagents with ketones, consistent with these data, is described.

Introduction

Although strong arguments have been made[1] to describe the mechanisms of "methylmagnesium bromide" ("CH_3MgBr") addition to 2-methylbenzophenone[2] (2-MBP) and benzonitrile[3] as proceeding via a polar pathway, evidence has been accumulating (since about 1968) to indicate that at least some Grignard reagent additions to ketones proceed via a single electron transfer (SET) pathway. ESR observations by Fauvarque and co-workers[4] in the reactions of R_2Mg compounds with fluorenone and benzophenone indicate that intermediate ketyls are formed and their concentrations depend on solvent polarity as well as upon the ability of the R group of the R_2Mg compound to stabilize a radical. In addition, Blomberg and Mosher[5] have shown that the reaction of "neopentylmagnesium chloride" with benzophenone in tetrahydrofuran (THF) yields not only 1,2-addition product (80%), but also benzopinacol and neopentane (each in ~20% yield). Both groups of workers conceived a mechanistic scheme such as that shown in eq I to explain these results.



More recently, Holm and Crossland have presented convincing evidence for a rate-determining SET step in the reaction of *tert*-butylmagnesium chloride ("*t*-C_4H_9MgCl") with benzophenone in diethyl ether.[6] In reactions with various substituted benzophenones, they obtained 1,2-addition products ranging from 0 to 55%, pinacol from 0 to 21%, 1,4-addition products from 0 to 39%, and 1,6-addition products from 0 to 100%. For all of these reactions, however, the Hammett plot of relative rate vs. σ-substituent constant gave a straight line (even when the substituted benzophenone had two or three *o*-methyl groups). In similar reactions using "CH_3MgBr" the presence of only one *o*-methyl group on benzophenone caused significant deviation from the linear free-energy relationship. Although, when added to acetone, "CH_3MgBr" reacts faster than "*t*-C_4H_9MgCl," Holm and Crossland have pointed out that "*t*-C_4H_9MgCl" reacts 100 times faster than "CH_3MgBr" toward benzophenone and 100 000 times faster toward the more sterically hindered duryl phenyl ketone. Based on this evidence, they proposed that the rate-determining step for the reaction of "*t*-C_4H_9MgCl" with benzophenone involves SET to give an intermediate common to all products (similar to eq 1). The SET is then followed by one or more fast steps to give the observed products. On the other hand, they considered it likely that the reaction of "CH_3MgBr" with benzophenone proceeds through a polar pathway.

Previous reports[2,3] from this research group have shown that the ratio of addition product to by-product (benzopinacol and benzhydrol), as well as the observed rate constants, in the reaction of "CH_3MgBr" with 2-MBP, depend upon the ratio of Grignard reagent to ketone, the "purity" of magnesium used to prepare the Grignard reagent, and the manner in which the Grignard was prepared (that is, using excess magnesium or excess methyl bromide in the preparation).[7] We were able to show that the amount of benzopinacol formed in the reaction of "CH_3MgBr" with benzophenone is directly proportional to the amount of transition metal impurity in the magnesium used to prepare the Grignard reagent and the amount of benzhydrol formed is due to the "MgH" impurity formed during the preparation of the Grignard reagent.[8]

In light of these observations, it is felt that the nature of the solvent, ketone, R group of the Grignard reagent, purity of the magnesium used to prepare the Grignard reagent, and mode of preparation of the Grignard reagent are all influential in determining the course of the reaction. It has also been recognized that the reactions of some Grignard reagents with ketones are highly influenced by the addition of some transition metal salts.[9] In this study we have investigated the influence of the above mentioned factors on the reactions of *tert*-butyl and methyl Grignard reagents with benzophenone, 2-methylbenzophenone, fluorenone, and acetone in various solvents. The purpose of this study, was to determine the relationship between polar and single electron transfer mechanisms in these

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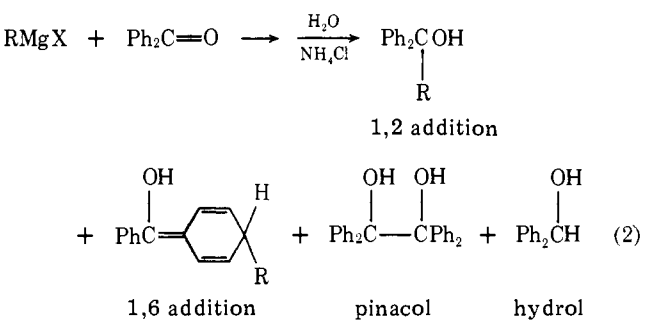
Table I. Reaction of "CH_3MgBr" with Benzophenone

Expt	Magnesium purity[a]	Grignard prepared in	Solvent	Grignard concn, M	G/K ratio	% 1,2 addn	% benzopinacol	% benzhydrol	$FeCl_3$ catalyst, ppm
1	GGT	xs[b] Mg	Ether	0.178	1.42	98.0	2.0	0	
2	SC	xs CH_3Br	Ether	0.213	1.17	>99.4	<0.6	0	
3	GGT	xs Mg	Ether	1.38	125	90.6	9.4	0	
4	SC	xs CH_3Br	Ether	0.048	0.05	>99.2	<0.8	0	
5	SC	xs CH_3Br	Ether	0.188	1.5	99.0	1.0	0	4
6	SC	xs CH_3Br	Ether	0.188	1.5	97.4	2.6	0	40
7	SC	xs CH_3Br	Ether	0.188	1.5	81.3	18.7	0	400
8	SC	xs CH_3Br	Ether	0.188	1.5	54.0	46.0	0	4 000
9	SC	xs CH_3Br	Ether	0.188	1.5	29.5	70.5	0	40 000
10	GGT	xs Mg	Ether	0.188	1.5	27.5	72.5	0	40 000
11	SC	xs CH_3Br	THF	0.188	1.5	99.2	0.8	0	
12	SC	xs CH_3Br	THF	0.188	1.5	27.0	72.0	<1.0	4 000
13	SC	xs CH_3Br	HMPA	0.187	1.5	96.6	0.8	2.6	4 000
14	SC	xs CH_3Br	HMPA	0.187	1.5	95.2	0.8	4.0	

[a] Key: GGT, Grignard grade turnings; SC, single crystal; G, Grignard; K, ketone. [b] xs, excess.

reactions, and the influence of the various factors on that relationship.

In the reaction of Grignard reagents with benzophenone, a number of products are observed, depending on the conditions (eq 2). Each of the products could be formed through a SET



pathway. While it is well known that 1,2 addition can be formed through a polar mechanism, it is less likely that the other products would be formed in that manner, especially benzopinacol, which has been demonstrated to be the coupling product of ketyl radical anions.[10] It appears likely, then, that a change in mechanism (or in the ratio of two competing mechanisms) in the reactions of Grignard reagents with ketones, could be monitored by a change in the ratio of products. Our initial investigation involved the influence of added transition metal salts on Grignard reactions with benzophenones in various solvents. The goal was to determine the influence of magnesium metal purity on the reaction pathway and to observe any effects due to solvent changes. Now an investigation has been made of Grignard reactions with both fluorenone and acetone. The object was to examine the influence of the reduction potential of the ketone on the reaction pathway. Finally, the effect of added *p*-dinitrobenzene (*p*-DNB) on the reaction of Grignard reagents with 2-methylbenzophenone (2-MBP) was studied. The goal was to determine the extent of SET in the Grignard reaction, especially along the pathway leading to 1,2-addition product.

Results and Discussion

Reactions of "CH_3MgBr" and *t*-BuMgCl with Benzophenone, Fluorenone, and Acetone. The reaction of excess CH_3Br with Ventron single-crystal magnesium (SC) followed by removal of the remaining CH_3Br has been shown to produce very little if any by-product when allowed to react with 2-methylbenzophenone. Kinetic studies with Grignard reagent prepared in this manner are devoid of anomalous behavior.[2,7b] On the other hand a Grignard reagent prepared from Grignard grade turnings (GGT) employing excess magnesium does not behave in a straightforward manner in its reactions with 2-methylbenzophenone. The "CH_3MgBr" prepared from single-crystal magnesium in excess CH_3Br (SC, excess CH_3Br) reacts with benzophenone (1.5 Grignard/ketone (G/K) ratio) in diethyl ether at room temperature to give >99.4% 1,2-addition product while the same reaction using the Grignard reagent prepared from Grignard turnings employing excess magnesium gives 98.5% 1,2-addition product (Table I). In the former case no benzopinacol was observed by NMR within the limits of detection, whereas in the latter case, 2% was observed. At higher G/K ratios larger amounts of by-product were observed. The reaction of 1.38 M "CH_3MgBr" (GGT, excess Mg) with 0.011 M benzophenone in diethyl ether (expt 3) gives only 90.6% 1,2-addition product and 9.4% benzopinacol. It would appear that there is some impurity in the Grignard reagent prepared from magnesium turnings whose effect is substantially increased depending on whether the Grignard reagent is prepared in excess CH_3Br or excess magnesium.

In the low G/K ratio reactions, when 0.188 M "CH_3MgBr" (SC, excess CH_3Br) was allowed to react with 0.125 M benzophenone in the presence of 4 to 40 000 ppm of $FeCl_3$ in diethyl ether, benzopinacol (1.0 to 70.5%) was observed in amounts proportional to the amount of catalyst added. Since no detectable by-product is formed in expt 2, whereas $FeCl_3$ causes significant quantities of by-product to be formed (expt 5–9), it appears that the presence of iron causes a considerable shift in the mechanism of the reaction.[11] Since "CH_3MgBr" (SC, excess CH_3Br) had been shown to react with benzophenone and 2-methylbenzophenone in a polar manner,[2,7b] and since benzopinacol may be expected to occur through a SET intermediate, it appears that the reaction of "CH_3MgBr" with benzophenone in diethyl ether normally proceeds via a polar mechanism except when catalyzed by a transition metal compound, at which time a SET pathway becomes predominant which results in the formation of benzopinacol.

Similar observations were made when the solvent was changed to THF. The reaction of 0.188 M "CH_3MgBr" (SC, excess CH_3Br) with 0.125 M benzophenone gave >99.2% 1,2-addition product and only <0.8% of the ketone was converted to benzopinacol (expt 11). On the other hand, when the benzophenone solution was doped with 4000 ppm of $FeCl_3$, benzopinacol accounted for 72.0% of the ketone and the 1,2 addition for only 27.0% (the other 1.0% was benzhydrol). As may have been expected, the more polar solvent (THF) better stabilized the ketyl intermediate which leads to benzopinacol; therefore, more benzopinacol was observed than in the equivalent experiment in diethyl ether.

Table II. Reaction of "CH_3MgBr" [a] (0.188 M) with Benzophenone (0.412 M) Doped with 4000 ppm of $FeCl_3$ in Diethyl Ether at Room Temperature in the Presence of Various Amounts of HMPA

Expt	HMPA, mmol	HMPA/G	% pinacol[b]	% 1,2 addn
1[c]	0	0	<0.6	99+
2[c]	0.17	0.184	<0.4	99+
3[c]	2.29	2.44	<1.0	99+
4	0	0	46.0	54.0
5	0.10	0.106	29.8	70.2
6	0.24	0.25	17.8	82.2
7	1.07	1.14	15.6	84.4
8[d]	1.07	1.14	15.1	84.9
9	2.17	2.31	<0.6	99+
10	2.45	2.61	<1.0	99+
11	5.09	5.42	<0.4	99+

[a] Made from single-crystal magnesium with excess CH_3Br. [b] Normalized: 100% = % pinacol + % hydrol + % addition. [c] No $FeCl_3$. [d] Inverse addition (ketone last).

The reaction of 0.188 M "CH_3MgBr" (SC, excess CH_3Br) with 0.125 M benzophenone in hexamethylphosphoramide (HMPA) appears to be proceeding through the same mechanism both in the presence and absence of $FeCl_3$ (i.e., no change in product ratios). This would seem to indicate no competition between polar and SET pathways in this solvent. Further investigation, however (Table II) shows that HMPA inactivates the iron catalyst. In the reaction of 0.188 M "CH_3MgBr" (SC, excess CH_3Br) with 0.412 M benzophenone in diethyl ether in the presence of 4000 ppm of $FeCl_3$, the addition of from 0 to 2.31 equiv of HMPA causes the amount of benzopinacol formed to fall from 46.0% to an undetectable amount (expt 4-9). Further increases in the amount of HMPA do not further affect the reaction (expt 10 and 11). It appears that the first 2 equiv of HMPA complexes the Grignard reagent (predominantly) and the iron is still free to catalyze SET. After all of the Grignard reagent has been complexed, however, the $FeCl_3$ is attacked by the HMPA and the subsequent complex is incapable of catalyzing SET. Therefore, the reaction of "CH_3MgBr" with benzophenone in the presence of more than 2 equiv of HMPA gives the same product analysis (Table II, expt 3 vs. expt 9-11) whether or not $FeCl_3$ is present because the mechanistic pathways involved in the two reactions are really the same ($FeCl_3$ is not actually involved in either).

Holm and Crossland have clearly demonstrated that the reaction of "*t*-C_4H_9MgCl" (prepared from Dow sublimed magnesium in excess Mg) with benzophenone proceeds predominantly, if not entirely, through a SET mechanism.[6] Since the purity of the magnesium was shown to be important in reactions of "CH_3MgBr," it was considered necessary to determine whether or not the findings of Holm were the result of a transition metal catalyzed reaction. We have found that the reaction of "*t*-C_4H_9MgCl" with benzophenone in diethyl ether gives from 48.0 to 50.0% conversion to 1,6-addition product, 38.2 to 42.3% conversion to 1,2-addition product, and 8.8 to 12.7% conversion to benzopinacol, regardless of the grade of Grignard reagent used, the ratio of G/K (if Grignard is in excess), or the presence of $FeCl_3$ (Table III). This is sufficient indication that the reaction of "*t*-BuMgCl" with benzophenone in diethyl ether proceeds predominantly through a SET mechanism even in the most favorable case for a polar mechanism, i.e., when the Grignard reagent is prepared from single-crystal magnesium in excess "*t*-C_4H_9Cl". Experiment 19 shows that, in a reaction which is already proceeding predominantly through SET, the presence of a more polar compound in the ether solvent (in this case the excess benzophenone) evidently stabilizes the ketyl radical anion and aids in escape from the solvent cage, forming a larger percentage of benzopinacol. In THF solvent, 41.3% 1,6-addition product, 47.0% 1,2-addition product, and 11.7% benzopinacol were formed. The same reaction in HMPA gave 26.0% 1,6-addition product, 72.3% 1,2-addition product, and 1.7% benzopinacol. No definitive conclusions can be drawn from the iron doped experiment in HMPA. The doped experiment in THF (expt 22) gives less 1,2-addition product than the undoped one (expt 21). This trend is in the right direction to indicate a shift away from a polar mechanism, but the magnitude of the change is too small to be significant and most likely the mechanism is SET in each case. The importance of the "*t*-BuMgCl"-$Ph_2C{=}O$ reaction lies in the fact that in ether the product: by-product ratio does not depend on the "purity" of the magnesium used to prepare the Grignard reagent. It appears, then, that the reaction, when compared with the work of Holm and Crossland,[6] proceeds through a SET mechanism, even when the best grade of magnesium available is used to prepare the Grignard.

Mechanism of Iron Catalysis. A study of the reaction of "CH_3MgBr" with benzophenone in the presence of large amounts of $FeCl_3$ or $FeCl_2$ shows an enlightening trend (Table IV). When "CH_3MgBr" and $FeCl_3$ are mixed in 1:1 ratio (expt 5), no reaction occurs with the benzophenone. It is readily apparent that, even as the $FeCl_3$ approaches this level (expt 1-4), the percent reaction with the benzophenone decreases. When "CH_3MgBr" and $FeCl_2$ are mixed in ratios approaching 1:1.1 (expt 6-8) no similar decrease in reaction with benzophenone is observed. This indicates that the species formed by the reduction of $FeCl_2$ with "CH_3MgBr" is capable of causing pinacol formation (or decomposing to a species capable of causing pinacol formation) while the species formed in the reduction of $FeCl_3$ is not. It is likely that the initial reaction between 1 equiv of "CH_3MgBr" and 1 equiv of $FeCl_3$ would

Table III. Reaction of "*t*-C_4H_9MgCl" with Benzophenone

Expt	Magnesium purity[a]	Grignard prepared in	Solvent	Grignard concn, M	G/K[b] ratio	% 1,6 addn	% 1,2 addn	% benzopinacol
15	SC	xs[c] *t*-C_4H_9Cl	Ether	0.188	1.5	48.0	42.3	9.7
16	GGT	xs Mg	Ether	0.188	1.5	50.0	40.3	9.7
17	GGT	xs Mg	Ether	0.188	20	48.5	40.7	10.8
18	GGT	xs Mg	Ether	0.230	121	50.0	42.2	8.8
19	SC	xs *t*-C_4H_9Cl	Ether	0.033	0.05	43.8	31.2	25.0
20	GGT	xs Mg[d]	Ether	0.188	1.5	49.1	38.2	12.7
21	SC	xs *t*-C_4H_9Cl	THF	0.208	1.68	41.3	47.0	11.7
22	SC	xs *t*-C_4H_9Cl[e]	THF	0.188	1.5	47.4	45.3	7.3
23	SC	xs *t*-C_4H_9Cl	HMPA	0.188	1.5	26.0	72.3	<1.7
24	SC	xs *t*-C_4H_9Cl[f]	HMPA	0.188	1.5	20.8	77.8	<1.4

[a] Key: GGT, Grignard grade turnings; SC, Ventron, single crystal. [b] G, Grignard; K, ketone. [c] xs, excess. [d] 400 ppm of $FeCl_3$. [e] 4000 ppm of $FeCl_3$ added. [f] 2500 ppm of $FeCl_3$, $CoCl_2$, CuCl, and $CrCl_3$ added.

Table IV. Reaction of "CH_3MgBr" (0.188 M) with Benzophenone (0.125 M) in Diethyl Ether at Room Temperature in the Presence of Large Quantities of $FeCl_3$ or $FeCl_2$ for 3 h

Expt	% $FeCl_3$	% $FeCl_2$	% $MgBr_2$	% pinacol[a]	% 1,2 addn[a]	% convn[b]
1	20	0	0	87.2	12.8	73.3
2	40	0	0	89.9	10.1	47.3
3	60	0	0	92.3	7.7	31.5
4	80	0	0	93.4	6.6	15.8
5	100	0	0	0	0	0
6	0	35	0	81.6	18.4	95.0
7	0	70	0	85.7	14.3	90.3
8	0	110	0	87.8	12.2	89.0
9	100	0	400[c]	87.5	12.5	36.0
10	100	0	225[d]	89.8	10.2	15.3

[a] Normalized such that % pinacol + % 1,2 addition = 100%. [b] 100%, unreacted ketone. [c] Equivalent Mg/Fe ratio to that of expt 1, Fe equivalent to that of expt 5. [d] Equivalent Mg/Fe ratio to that of expt 2, Fe equivalent to that of expt 5.

Table V. Reaction of Grignard Reagents (0.940 mmol) with Fluorenone (0.627 mmol) in Diethyl Ether (5.00 ml) for 4 h

Expt	Grignard reagent	HMPA added, mL	$FeCl_3$, ppm	% addn[a]	% 1,6 addn	% pinacol	% hydrol
1	CH_3MgBr[b]	0	0	100	0	0	0
2	CH_3MgBr	0	4000	76.5	0	29.4	0
3	CH_3MgBr	5	0	99.2	0	0.8	0
4	t-C_4H_9MgCl[c]	0	0	74.8	15.4	9.8	0
5	t-C_4H_9MgCl	0	4000	75.8	13.2	11.0	0
6	t-C_4H_9MgCl	5	0	93.6	6.4	0	0

[a] Normalized: 100% = % 1,2 addition + % 1,6 addition + % pinacol + % hydrol. [b] CH_3MgBr prepared from excess magnesium (Ventron chips, 99.99%). [c] t-BuMgCl prepared from 1:1 t-BuCl/magnesium (Ventron chips, 99.99%).

involve exchange to give $[CH_3FeCl_2]$ (eq 3) followed by homolytic decomposition to give hydrocarbons plus an iron(II) species (eq 4).

$$\text{"}CH_3MgBr\text{"} + FeCl_3 \rightarrow [CH_3Fe^{III}Cl_2] + MgBrCl \quad (3)$$

$$[CH_3Fe^{III}Cl_2] \rightarrow CH_4 + CH_3CH_3 + CH_2{=}CH_2, \text{ etc.} + [Fe^{II}Cl_2] \quad (4)$$

If this is the case, then neither $[CH_3Fe^{III}Cl_2]$ or the iron(II) species is capable of transferring an electron to the ketone to form the ketyl (and subsequently pinacol upon hydrolysis). It is equally apparent that if $[CH_3Fe^{III}Cl_2]$ is formed, it is not capable of addition to the ketone (possibly it decomposes too quickly to react) and that the reaction of "CH_3MgBr" with $FeCl_3$ occurs too quickly for any reaction of "CH_3MgBr" with benzophenone to occur since no 1,2-addition product is observed (Table X, expt 5).

On the other hand, it is likely that the initial reaction between 1 equiv of "CH_3MgBr" and 1 equiv of $FeCl_2$ would involve exchange to give $[CH_3Fe^{II}Cl]$ (eq 5) followed by homolytic decomposition to give hydrocarbons plus an iron(I) species (eq 6).

$$\text{"}CH_3MgBr\text{"} + FeCl_2 \rightarrow [CH_3Fe^{II}Cl] + MgClBr \quad (5)$$

$$[CH_3Fe^{II}Cl] \rightarrow CH_4, CH_3CH_3, CH_2{=}CH_2, \text{ etc.} + [Fe^{I}Cl] \quad (6)$$

If this is the case, either $[CH_3Fe^{II}Cl]$ or the iron(I) species transfers an electron to the ketone to form the ketyl (and subsequently pinacol upon hydrolysis). Since the iron(II) species postulated above (eq 4) did not lead to pinacol, it seems unlikely that $[CH_3Fe^{II}Cl]$ would be capable of electron transfer either. This implicates the iron(I) species (eq 6) as the active agent leading to pinacol formation. Those Grignard reactions with benzophenone in the presence of only a small amount of iron could recycle this agent in a catalytic manner (eq 7 and 8).

$$[Fe^{I}Cl + Ph_2C{=}O \rightarrow Ph_2\dot{C}O^{-}[Fe^{II}Cl]^{+} \quad (7)$$

$$CH_3MgBr + Ph_2\dot{C}O[Fe^{II}Cl]^{+} \rightarrow Ph_2\dot{C}O^{-}MgBr + [CH_3Fe^{II}Cl] \quad (8)$$

The results in Table IV (expt 8) also indicate 1,2 addition among the products of the reaction of "CH_3MgBr" with benzophenone in the presence of 1 equiv of $FeCl_2$. There are two possible pathways whereby this could occur: $[CH_3Fe^{II}Cl]$ could react directly with ketone to give 1,2-addition product (if the iron species does not decompose more rapidly than it adds to the ketone) or the rate of reaction of "CH_3MgBr" with $FeCl_2$ may be too slow to eliminate completely direct Grignard reagent addition to the ketone. In light of the apparently rapid decomposition of the $[CH_3Fe^{III}Cl_2]$ species it seems that the latter possibly may be the more likely.

The addition of large amounts of $MgBr_2$ to the reaction of "CH_3MgBr" with benzophenone in the presence of 1 equiv of $FeCl_3$ increases the amount of reaction observed (Table IV, expt 9 and 10). This implies that the active pinacol producing agent also involves magnesium, further complicating the mechanistically simple description shown in eq 3-8.

Since the reduction potential of the ketone involved should play a large role in determining the amount (if any) of SET involved in Grignard reactions, fluorenone (reduction potential = −1.29 V vs. SCE in DMF) and acetone (reduction potential = −2.46 V vs. SCE in 75% dioxane/H_2O) reactions with methyl and *tert*-butyl Grignard reagents were compared with those reactions already studied wth benzophenone (reduction potential = −1.72 V vs. SCE in DMF). It is apparent from Table V that the reactions of Grignard reagents with fluorenone are qualitatively very similar to those with benzophenone. The reaction of "CH_3MgBr" with fluorenone in the presence of 4000 ppm of $FeCl_3$ (expt 2) shows less pinacol formation than the same reaction with benzophenone (29.4% vs. 46.0%). The reaction of "t-C_4H_9MgCl" with fluorenone (expt 4) shows about the same amount of pinacol as a similar

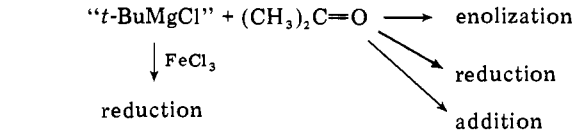
Table VI. Reaction of Grignard Reagents (0.093 M) with Acetone (0.063 M) in Diethyl Ether at Room Temperature

Expt	Grignard reagent	Grade of Mg[a]	$FeCl_3$, ppm	Reaction time, min(s)	% 1,2 addn	% redn	% pinacol	% acetone[b]
1	CH_3MgBr	GGT[c]	0	20	100	0	0	0
2	CH_3MgBr	49's[d]	0	20	100	0	0	0
3	CH_3MgBr	DS[c]	0	20	100	0	0	0
4	CH_3MgBr	GGT	4000	20	100	0	0	0
5	CH_3MgBr	49's	4000	20	100	0	0	0
6	CH_3MgBr	DS	4000	20	100	0	0	0
7	t-C_4H_9MgCl[e]	GGT	0	20	55.6	15.7	0	28.7
8	t-C_4H_9MgCl	DS	0	20	62.1	8.4	0	29.5
9	t-C_4H_9MgCl	GGT	4000	20	5.1	87.8	0	7.1
10	t-C_4H_9MgCl	DS	4000	20	17.1	73.9	0	9.0
11	t-C_4H_9MgCl	DS	0	(10)	20.4	0.5	0	79.2
12	t-C_4H_9MgCl	DS	0	(21)	28.4	2.4	0	69.2
13	t-C_4H_9MgCl	DS	0	(50)	37.6	3.2	0	59.1
14	t-C_4H_9MgCl	DS	0	(60)	40.4	4.6	0	55.0
15	t-C_4H_9MgCl	DS	0	(120)	49.7	4.4	0	45.9
	t-C_4H_9MgCl	DS	4000	(6)	12.3	23.3	0	64.4
17	t-C_4H_9MgCl	DS	4000	(9)	11.8	28.1	0	60.0
18	t-C_4H_9MgCl	DS	4000	(28)	18.1	62.3	0	19.7
19	t-C_4H_9MgCl	DS	4000	(60)	16.0	74.0	0	10.0
20	t-C_4H_9MgCl	DS	4000	(120)	17.9	76.2	0	5.9

[a] GGT, Grignard grade turnings; 49's, Ventron chips (99.99%); DC, Dow, doubly sublimed. [b] In 20-min reactions this corresponds to % enolization. In shorter reactions it also includes unreacted ketone. [c] Made from excess magnesium. [d] Made from excess CH_3Br. [e] All t-C_4H_9MgCl reagents were made from 1:1 magnesium/t-BuCl.

reaction with benzophenone (9.8% vs. 9.7%) but more 1,2 addition and less 1,6 addition (74.8 and 15.4% vs. 42.3 and 48.0%). Both sets of results can be easily explained in terms of steric bulk at the reaction site in that fluorenone is less sterically encumbered at the carbonyl group than benzophenone. In the case of "CH_3MgBr" addition to fluorenone, 1,2 addition is thus able to compete more favorably with iron catalyzed pinacol formation and, in the case of "t-C_4H_9MgBr," coupling at the 2 position takes place more rapidly than coupling at the 6 position. The relative amount of diffusion to form pinacol in the "t-C_4H_9MgCl" case is apparently about the same with each ketone since about the same amount of pinacol is observed in each case. The effect of $FeCl_3$ catalyzed Grignard addition to fluorenone is qualitatively similar to that observed with benzophenone: it causes pinacol formation in the methyl Grignard reactions and has no effect in *tert*-butyl Grignard reactions. The effect of HMPA on these reactions is also qualitatively the same as with benzophenone: HMPA favors 1,2 addition with *tert*-butyl Grignards and has little effect upon the methyl Grignard reactions. Qualitatively similar results have been obtained from ketones and quinones of even lower reduction potential.[12]

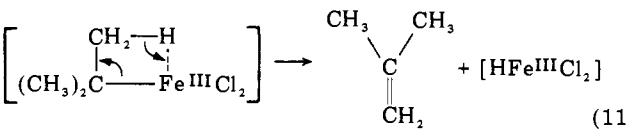
Reactions of Grignard reagents with acetone have resulted in a trend different from the one observed with benzophenone and fluorenone. This reaction of 0.093 M "CH_3MgBr" with 0.063 M acetone in diethyl ether results in only 1,2-addition product regardless of the grade of magnesium, the mode of Grignard reagent preparation, or the addition of 4000 ppm of $FeCl_3$ (Table VI, expt 1-6). Apparently the reduction potential of the acetone is high enough that the iron species from the reaction of "CH_3MgBr" with $FeCl_3$ which would be expected to generate pinacol is unable to transfer an electron to the ketone. The reaction of "t-C_4H_9MgCl" with acetone, on the other hand, shows variations depending on the $FeCl_3$ content of the reaction. When no $FeCl_3$ is added (expt 7 and 8) the percent 1,2 addition varies from 55.6 to 62.1%, the percent reduction varies from 15.7 to 8.4%, and the percent enolization varies from 28.7 to 29.5% (depending on the purity of the magnesium used to prepare the Grignard reagent). In the presence of 4000 ppm of $FeCl_3$, however, the percent 1,2 addition varies from 5.1 to 17.1%, the percent reduction from 87.8 to 73.9%, and the percent enolization from 7.1 to 9.0%. (This variation is likely due to the difference in transition metal content of DS vs. GGT magnesium.) It could be that while "CH_3MgBr," "$CH_3MgBr + FeCl_3$," and "t-C_4H_9MgCl" are unable to donate an electron to a ketone with a reduction potential as high as that of acetone, "t-$C_4H_9MgCl + FeCl_3$" is capable of such SET. On the other hand, it is also possible that an intermediate iron hydride species formed through the reaction of "t-C_4H_9MgCl" with $FeCl_3$ is rapidly reacting with the acetone in competition with the normal Grignard reaction (eq 9). The



(9)

initially formed species in the reaction of "t-C_4H_9MgCl" with $FeCl_3$ could be [t-$C_4H_9Fe^{III}Cl_2$] (eq 10) which may be expected to decompose by β-hydrogen elimination to give an intermediate iron hydride species (eq 11). It is likely that such a species would be capable of reducing acetone (eq 12).

$$t\text{-}C_4H_9MgCl + FeCl_3 \rightarrow [t\text{-}C_4H_9Fe^{III}Cl_2] + MgCl_2 \rightarrow \quad (10)$$



(11)

$$[HFe^{III}Cl_2] + (CH_3)_2C{=}O \rightarrow (CH_3)_2CHOFeCl_2 \quad (12)$$

$$(CH_3)_2CHOFeCl_2 + MgCl_2 \rightarrow FeCl_3 + (CH_3)_2CHOMgCl \quad (13)$$

A relative rate study of the reaction of "t-C_4H_9MgCl" with acetone in the presence or absence of 4000 ppm of $FeCl_3$ (Table VI, entries 11-20) casts some light on the above suggestions. The 20-min samples (entries 8 and 10) were used to determine the relative % enolization:1,2-addition ratio for each reaction: 0.526 for the iron catalyzed reaction and 0.457 for the uncatalyzed reaction. Assuming that in each of these reactions the percent enolization is a constant fraction of the percent 1,2 addition (with time), the plots of percent unreacted acetone vs. time seen in Figure 1 were constructed. It is readily

Table VII. Reaction of "CH_3MgBr" (0.600 M) in the Presence of "Trapping Agents" (0.100 M) in Diethyl Ether at Room Temperature[a]

Expt	Trapping agent	[2-MPB], M	% $FeCl_3$	% pinacol[b]	% 1,2 addn	% recovd 2-MBP	% recovd trap
1	Styrene	0	0				76.1[c]
2	Styrene	0	1.73				26.8[c]
3	Styrene	0.100	0	0	100	0	67.0[c]
4	Styrene	0.100	1.73	94.7	5.3	0	27.1[c]
5	*p*-DNB[d]	0	0				57.0
6	*p*-DNB	0	1.73				47.6
7	*p*-DNB	0.100	0	0	96.3	3.7	43.1
8	*p*-DNB	0.100	1.73	39.6	23.6	36.8	33.3
9	None	0.100	0	0	100	0	
10	None	0.100	1.73	96.3	3.7	0	

[a] Reaction time 3 h. [b] Normalized: 100% = % pinacol + % 1,2 addition. [c] No products corresponding to propylbenzene. [d] *p*-Dinitrobenzene.

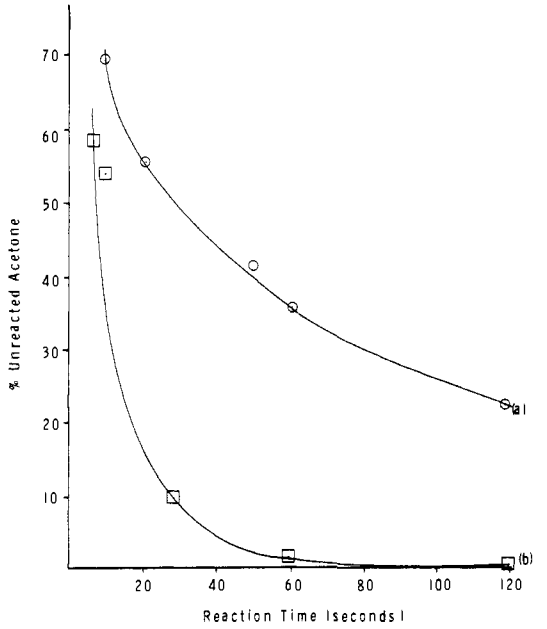


Figure 1. (a) Reaction of "t-C_4H_9MgCl" (0.093 M) with acetone (0.063 M). (b) Reaction of "t-C_4H_9MgCl" (0.093 M) with acetone (0.063 M) in the presence of 4000 ppm of $FeCl_3$. Both reactions were carried out in diethyl ether at room temperature.

apparent that the iron catalyzed reaction is quite a bit faster than the uncatalyzed one.

From Figure 1 it can be determined that the half-life of the reaction of 0.093 M "t-C_4H_9MgCl" with 0.063 M acetone in the presence of 4000 ppm of $FeCl_2$ is ~10 s and the half-life of the same reaction without $FeCl_3$ is ~30 s. The significance of this observation is that, although the iron catalyzed reaction is about three times as fast as the uncatalyzed one, it produces only about one-third as much 1,2-addition product and about one-third as much enolization. It seems that the real difference between the two reactions is a competition such as the one involved in eq 9. The rates of 1,2 addition and of enolization are unaffected by the addition of the $FeCl_3$. However, in the presence of $FeCl_3$, a species is formed (presumably an iron hydride) which rapidly reduces the acetone via a pathway in competition with the normal Grignard reaction. (More will be said about this intermediate later in this paper.)

The reduction potential of the ketone has, therefore, been shown to be an important factor in these reactions. This especially appears to be so when considering reactions in which iron intermediates are proposed. "CH_3MgBr" seems to react with benzophenone, fluorenone, and acetone in a polar manner. In the presence of $FeCl_3$, however, "CH_3MgBr" produces a species which is capable of transferring an electron to benzophenone and fluorenone but not acetone. On the other hand, "t-C_4H_9MgCl" seems to react with benzophenone and fluorenone through a SET pathway and with acetone through a polar pathway. Ferric chloride interacts with "t-C_4H_9MgCl" to produce a species which is unable to compete with Grignard addition to benzophenone and fluorenone, but which reacts about three times as fast as the Grignard reagent with acetone. Presumably this is an iron hydride species and its reaction with acetone is polar. It is apparent, in any case, that the 1,2-addition product formed by the reaction of "t-C_4H_9MgCl" with acetone comes about via a polar pathway in both the presence and absence of $FeCl_3$.

Trapping the Radical Anion with *p*-Dinitrobenzene. The most significant question that remains to be answered concerning the mechanism of Grignard reagent addition to ketones is the nature of the alkyl transfer in the absence of by-product producing impurities. From the work of Holm and Crossland[6] (and the work reported here, Table III), it is apparent that the reaction of "t-C_4H_9MgCl" with benzophenone proceeds through a SET pathway represented by Holm in the following manner:

$$t\text{-BuMgCl} + Ph_2C{=}O \rightarrow [Ph_2\dot{C}O^-]MgBr^+ + t\text{-Bu}\cdot \rightarrow \text{products} \quad (14)$$

In the reaction of "CH_3MgBr" with benzophenone the reaction pathway is much less obvious. While the SET pathway could indeed be operative (with the rate of collapse to give 1,2-addition product greatly exceeding the rate of $CH_3\cdot$ diffusion to produce pinacol), there is no real evidence to indicate that the pathway is not polar. The ability to "trap" this radical anion intermediate (or the species which has just donated the electron, *i.e.*, the radical) would be instrumental in determining which mechanism may be involved.

With this in mind, styrene and *p*-dinitrobenzene were screened as possible "trapping agents" in the reaction of "CH_3MgBr" with 2-MBP (Table VII). Styrene was not effective as a "trap." No products corresponding to C_6H_5-C_3H_7 were obtained. The styrene did polymerize more in the iron catalyzed reaction than in the uncatalyzed reaction, but this was true whether or not 2-MBP was present. Styrene had no effect on the expected product distribution. On the other hand, *p*-DNB did seem to have some effect on the reaction. The reaction without iron catalyst (expt 7) was incomplete. Under the same conditions, this reaction without *p*-DNB went to completion (expt 9). The iron catalyzed reaction (expt 8) gave much less pinacol than was observed under the same conditions without *p*-DNB (expt 10) and again failed to proceed to completion.

Kornblum and coworkers[13] have pointed out that *p*-DNB is effective as a "radical anion scavenger" which can "short-circuit" SET reactions. Preliminary results (Table VII) indicated that *p*-DNB may be useful in probing Grignard reactions with ketones. If the Grignard reaction involves the process

Table VIII. Reaction of Grignard Reagents with 2,2'-Dimethylbenzopinacol in the Presence or Absence of *p*-Dinitrobenzene

Expt	Grignard reagent	[Grignard], M	[Pinacol], M	[*p*-DNB], M	Reaction time, h	Products[a] % 1,2 addn	% pinacol	% ketone	% hydrol	% *p*-DNB recovd
1	*t*-C_4H_9MgCl	0.300	0.013	0	70	0	100	0	0	
2	CH_3MgBr	0.300	0.013	0	70	0	100	0	0	
3	CH_3MgBr	0.050	0.025	0.050	3	0	72.6	27.4	0	79.2
4	CH_3MgBr	0.300	0.025	0.050	3	42.4	51.2	6.3	0	12.3

[a] Normalized: 100% = % 1,2 addition + % pinacol + ketone + % hydrol.

Table IX. Reaction of Grignard Reagents Which Have Been in Contact with *p*-Dinitrobenzene for 30 min Prior to Addition of 2-MBP in Diethyl Ether at Room Temperature

Expt	Grignard reagent	[RMgX], M	[*p*-DNB], M	[2-MBP], M	Products[a] % 1,2 addn	% pinacol	% 1,6 addn	% ketone	% recovd *p*-DNB	RMgX/*p*-DNB[b] used
1[c]	CH_3MgBr	0.287	0.048	0.048	100	0	0	0	36.7	
2[d]	CH_3MgBr	0.092	0.015	0.092	56.6	0	0	43.4	26.9	3.56
3[c]	*t*-C_4H_9MgCl	0.287	0.048	0.048	14.3	0	~77.2	~8.5	4.9	5.77
4[d]	*t*-C_4H_9MgCl	0.092	0.015	0.092	1.4	0	~4.1	~94.6	0.0	5.68

[a] Normalized: 100% = % 1,2 addition + % pinacol + % 1,6 addition + % ketone. [b] Millimoles of Grignard reagent used, but not accountable in products divided by millimoles of *p*-DNB used. [c] Reaction time 3 h. [d] Reaction time 21 h.

Table X. Reaction of "CH_3MgBr" [a] with 2-MBP (0.0167 M) in the Presence or Absence of *p*-Dinitrobenzene in Diethyl Ether at Room Temperature. A Pseudokinetic Study

Expt	["CH_3MgBr"], M	% *p*-DNB	Reaction time, min	% 1,2 addn[b]	% pinacol	% recovd ketone	% recovd *p*-DNB
1	0.033[c]	0	3	23.9	Trace	76.1	
2	0.033	0	9	41.4	4.1	54.9	
3	0.033	0	16	58.6	10.5	31.0	
4	0.033	0	30	63.9	13.1	23.0	
5	0.100	17	5	57.2	0	42.8	17.8
6	0.100	17	11	79.6	0	20.4	15.6
7	0.100	17	20	91.9	0	8.1	19.4
8	0.100	17	40	98.7	0	1.3	13.9

[a] Dow doubly sublimed magnesium contaminated by a few parts per million of $FeCl_3$ or other transition metal salt. [b] Normalized: 100% = % 1,2 addition + % pinacol + % ketone. [c] This provides about the same Grignard concentration as exists in the *p*-DNB doped reactions considering how much is used up in the reaction with the *p*-DNB.

described by eq 15, it should be possible for *p*-DNB to intervene as described by eq 16 and 17.

$$RMgX + Ph_2C{=}O \rightarrow [RMgX]^{+\cdot} + [Ph_2\dot{C}O^-] \rightarrow \text{products} \quad (15)$$

$$p\text{-DNB} + [Ph_2\dot{C}O^-] \rightarrow Ph_2C{=}O + [p\text{-DNB}]^{-\cdot} \quad (16)$$

$$[RMgX]^{+\cdot} + [p\text{-DNB}]^{-\cdot} \rightarrow RMgX + p\text{-DNB} \quad (17)$$

Thus the materials are regenerated and the reaction is "short-circuited." It would be possible for SET products to "leak" through the circuit depending on the relative rates of reactions 18–20.

$$p\text{-DNB} + [Ph_2CO] \longrightarrow [p\text{-DNB}]^{\cdot} + Ph_2C{=}O \quad (18)$$

$$[Ph_2CO^-] + [Ph_2CO^-] \longrightarrow Ph_2C(O^-)\text{—}CPh_2(O^-) \quad (19)$$

$$[Ph_2CO^-] + [RMgX]^{+} \longrightarrow Ph_2C(R)OMgX \quad (20)$$

Step 16 above shows that *p*-DNB should be capable of removing an electron from the ketyl to regenerate the ketone. This concept was easily tested by the experiments described in Table VIII. The reaction of excess Grignard reagent with pinacol produces the ketyl, but does not react further. The only product upon subsequent hydrolysis is the starting pinacol (expt 1 and 2). However, when pinacol is allowed to react with an equivalent amount of Grignard reagent in the presence of *p*-DNB, 27.4% ketone is recovered upon hydrolysis (expt 3). If a 6:1 excess of the Grignard reagent is used, 42.4% 1,2-addition product, as well as 6.3% ketone, is recovered (expt 4). It is clear from these data that *p*-DNB is indeed capable of removing the electron from the ketyl radical anion to regenerate the ketone although not with 100% efficiency.

It had been noticed in the reactions involving *p*-DNB so far, that the *p*-DNB is never quantitatively recovered. This is undoubtedly due to a side reaction in which the *p*-DNB reacts directly with the Grignard reagent. Table IX shows the results of a study to determine how much of the Grignard reagent is used up by the *p*-DNB in this process. Apparently ~4 mol of "CH_3MgBr" and 6 mol of *t*-C_4H_9MgCl react with each mole of *p*-DNB. Obviously, then, one of the effects of *p*-DNB on Grignard reactions with ketones is to remove some of the Grignard from the reaction, thus often leading to incomplete consumption of the ketone.

Based on this information, a study was carried out to determine the effect of *p*-DNB on the rate of the reaction of "CH_3MgBr" with 2-MBP (Table X, Figure 2). The reaction conditions were chosen such that after all the Grignard reacted with *p*-DNB (in experiments 5–8) there would still be as much

Table XI. Reaction of "t-C_4H_9MgCl" with 2-MBP (0.0167 M) in the Presence or Absence of p-DNB in Diethyl Ether at Room Temperature

Expt	["t-C_4H_9MgCl"], M	% p-DNB	Reaction time, min	% 1,6 addn[a]	% 1,2 addn	% pinacol	% recovd ketone	% recovd p-DNB
1	0.033[b]	0	3	71.2 (78.4)[c]	19.6 (21.6)	9.1	0	
2	0.033	0	6	76.4 (83.7)	14.9 (16.3)	8.7	0	
3	0.033	0	9	73.5 (79.7)	18.7 (20.3)	7.8	0	
4	0.033	0	18	74.2 (83.5)	14.7 (16.5)	11.2	0	
5	0.133	12.5	4	83.0	17.0	0	0	0
6	0.133	12.5	7	84.3	15.7	0	0	3.1
7	0.133	12.5	16	84.0	16.0	0	0	4.6
8	0.133	12.5	29	85.0	15.0	0	0	10.5

[a] Normalized: 100% = % 1,6 addition + % 1,2 addition + % pinacol + % ketone. [b] Provides the same effective Grignard concentration considering the reaction between "t-BuMgCl" and p-DNB. [c] Normalized: 100% = % 1,6 addition + % 1,2 addition.

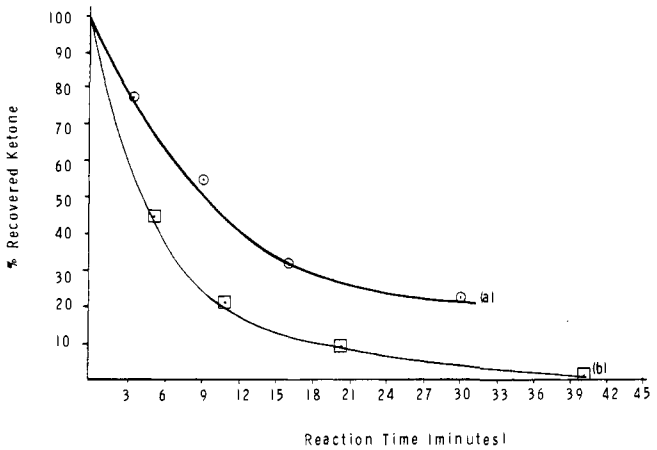


Figure 2. (a) Reaction of "CH_3MgBr" (0.033 M) with 2-MBP (0.0167 M) in diethyl ether at room temperature. (b) Reaction of "CH_3MgBr" (0.100 M) with 2-MBP (0.0167 M) in the presence of 17% p-DNB in diethyl ether at room temperature.

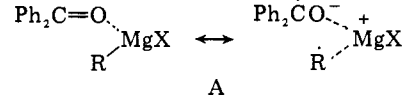
Grignard left as in the reactions without p-DNB (expt 1-4). (It is important to note that this is a very qualitative correction, but one which provides a valid experiment. Initially, of course, the reaction which contains p-DNB will have a much higher Grignard reagent concentration than the equivalent reaction without p-DNB. If p-DNB has no significant effect on the reaction of "CH_3MgBr" with benzophenone, then the rate of the p-DNB-containing reaction will be somewhat greater than the rate of the reaction in the absence of p-DNB, reflecting the initially higher Grignard reagent concentration in the former reaction. If, however, p-DNB does significantly intervene in the reaction of "CH_3MgBr" with benzophenone, a significant decrease in the rate of the reaction in the presence of p-DNB should be observed relative to the rate of the reaction in the absence of p-DNB.) It is apparent that the reaction of "CH_3MgBr" with 2-MBP in the presence of p-DNB is not significantly slower than that same reaction without p-DNB. (In fact, under the conditions chosen, the p-DNB containing reaction was actually slightly faster.) In any case, the important feature of this set of reactions is that p-DNB completely eliminates pinacol formation. It appears that the p-DNB abstracts the electron from the ketyl to regenerate the starting ketone. The fact that the p-DNB cannot do the same to the 1,2-addition product is indicative of a difference in the mechanism leading to these two products.

An experiment similar to the experiment carried out with "CH_3MgBr" was conducted to dertermine the effect of p-DNB on the reaction of "t-C_4H_9MgCl" with 2-MBP (Table XI). Both reactions were too fast for the methods of measurement that were used; however, this rapid rate in itself is enough to assure that p-DNB does not significantly slow the rate of the reaction of "t-C_4H_9MgCl" with 2-MBP. The most impressive observation again concerns the formation of pinacol. While there is no pinacol formed in the p-DNB-influenced reaction compared with 9.2 ± 1.4% formed in the absence of p-DNB, the ratios of 1,6-addition:1,2-addition products in the two reactions are identical (within experimental error). In the reaction of "t-C_4H_9MgCl" with 2-MBP, the ratio of 1,6-addition:1,2-addition product is 84.1 ± 0.8:15.9 ± 0.8% while in the absence of p-DNB the ratio is 81.3 ± 2.7:18.7 ± 2.7%. These results indicate that there is some difference in the mechanism of formation of pinacol compared with the formation of 1,2- and 1,6-addition products. The logical suggestion is that the pathway to pinacol formation must necessarily involve the "free ketyl" which is susceptable to electron transfer to p-DNB. By analogy, then, the pathways leading to 1,2 and 1,6 addition must not involve "free ketyl." To be consistent with these new data, it seems necessary for the mechanism of the reaction of "t-C_4H_9MgCl" with 2-MBP, to involve a radical anion-radical cation pair which can collapse to addition products or dissociate to form t-Bu· and pinacolate as described by eq 21.

$$t\text{-}C_4H_9MgCl + Ph_2C{=}O \xrightarrow{\text{SET}} [Ph_2\dot{C}O^-][t\text{-}C_4H_9MgCl]^{+\cdot} \begin{cases} \xrightarrow{} \text{1,2 addition} \\ \xrightarrow{} \text{1,6 addition} \\ \xrightarrow{} [Ph_2\dot{C}OMgCl] + t\text{-}C_4H_9\cdot \end{cases} \quad (21)$$

pinacol $\quad$ t-C_4H_{10} (solvent)

This radical anion-radical cation pair (A) may be thought of as originating via the σ complex which is undoubtedly formed very rapidly in a simple acid-base reaction. The



A

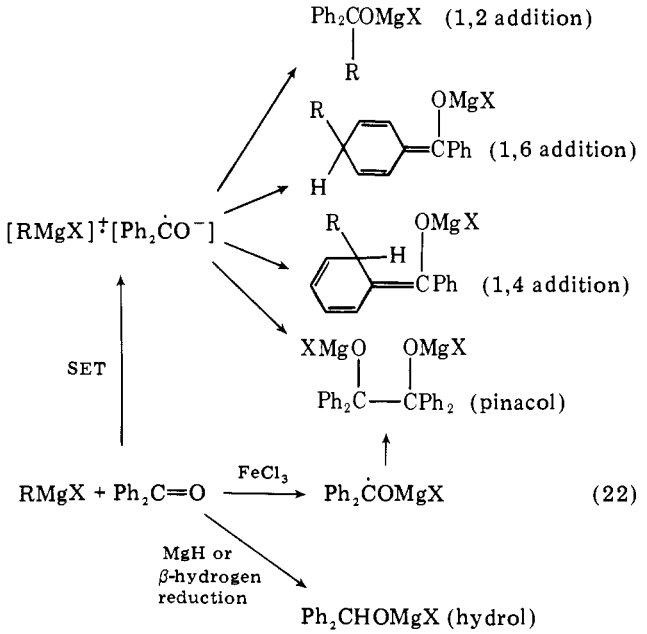
tightness or looseness of this complex would undoubtedly be affected by the stability of the incipient radical, R·. This would in turn affect the amount of SET character observed in the reaction. It is possible, then, that all Grignard reactions with ketones proceed via this pathway. With *tert*-butyl Grignard reagents, the complex is very loose owing to the stability of the t-Bu· radical. Thus SET character is observed in the reaction, including the dissociation of the complex to give ketyl, which dimerizes to form pinacol. The methyl Grignard on the other hand, should form a tighter complex which bears only some resemblence to a radical anion-radical cation pair. This complex could collapse to give only 1,2-addition product too rapidly for anything else to occur (like diffusion of CH_3· to give pinacol). According to this picture, pinacol formation, in the case of methyl Grignard reactions with benzophenones, would

Table XII. Reaction of "CH_3MgBr" (0.150 M) with 2-MBP or Benzophenone (0.100 M) in the Presence of Various Amounts of $FeCl_3$ in Diethyl Ether at Room Temperature for 3 h

Expt	Ketone	$FeCl_3$, ppm	% 1,2 addn[a]	% pinacol
1	2-MBP	4 000	45.3	54.7
2	2-MBP	40 000	23.7	76.3
3	$Ph_2C{=}O$	000	56.8	43.2
4	$Ph_2C{=}O$	40 000	30.6	69.4

[a] Normalized: 100% = % 1,2 addition + % pinacol.

be viewed as a separate reaction influenced only by traces of transition metal contaminants. The overall mechanism for Grignard reactions with benzophenones could be expressed by eq 22. Hydrol would normally be formed only when the R group has β hydrogens and when other factors are favorable (i.e., steric bulk, reduction potential, radical stabilities, etc.) or when -MgH species are present in the Grignard reagent.[14] Pinacol would occur both from dissociation of the radical



anion-radical cation pair (e.g. when R = t-C_4H_9) and from direct action of an iron-magnesium species on the ketone (e.g. when R = Me). All other products would come about only through the radical cation-radical anion pair.

The reaction of "t-C_4H_9MgCl" with benzophenones apparently occurs only by the SET pathway, even in the presence of $FeCl_3$. Most likely the rate of reaction along this pathway greatly exceeds that along the other pathways owing to the reduction potential of the ketone and the radical stability of the R group of the Grignard reagent. Another factor, however, may be the mode of decomposition of the initially formed species in the reaction of "t-C_4H_9MgCl" with $FeCl_3$. As has been previously discussed, this t-C_4H_9Fe species would be expected to give an -FeH intermediate by olefin elimination (before further decomposition). This -FeH species may not be as apt to transfer an electron as the one formed by the homolytic decomposition product of a CH_3Fe- compound. It is also reasonable that the -FeH intermediate could be stable enough to tie up the iron until the Grignard reaction with the ketone is effectively over. It may be of interest to point out that the reaction of "neopentylmagnesium bromide" with benzophenone in diethyl ether in the presence of trace amounts of $FeCl_3$ leads almost exclusively to pinacol formation while the same reaction in the absence of $FeCl_3$ leads equally exclusively to 1,2-addition product. A neopentyliron species, like a methyliron species, would be incapable of olefin elimination to give an iron hydride compound, and so would be expected to decompose via a homolytic pathway. Thus both methyl and neopentyl Grignard reagents apparently react with iron to give species which are incapable of olefin elimination but which lead to pinacol formation, whereas *tert*-butyl Grignard reagents may react to give a species which would decompose via olefin elimination to give an iron hydride intermediate, but which does not lead to pinacol formation. While this observation proves nothing, it does lend credibility to the suggestion made about the existence and reactivity of an iron hydride species.

If the above mechanistic picture (described by eq 22) is valid, steric factors in the vicinity of the reaction site would be expected to show up in the product distribution of the reaction of "CH_3MgBr" with benzophenones in the presence of $FeCl_3$. Table XII shows that this is so. The reaction with 2-MBP in the presence of 4000 ppm of $FeCl_3$ shows 11.5% more pinacol than the same reaction with benzophenone. This would have been predicted since the addition reaction has the largest steric requirement and therefore would occur at a slower rate in the reaction with the bulkier ketone. The rate of electron transfer from the iron species to produce pinacol would not be nearly so affected by steric bulk, so that SET woul occur at about the same rate with each ketone. It appears from expt 2 and 4 that this effect is less noticeable at higher iron concentration (only 6.9% difference with 40 000 ppm of Fe).

Conclusion

The mechanism of Grignard reactions with ketones is dependent on a variety of factors. The nature of the alkyl group of the Grignard reagent is probably the most important single factor involved in determining the extent of SET to be observed in the reaction with a given ketone. The purity of the magnesium used to prepare the Grignard reagent as well as the method of Grignard preparation has been shown to dramatically affect the reaction with ketones. The reduction potential of the ketone and the nature of the solvent in which the reaction is carried out are also important factors. It is apparent that reaction of "t-C_4H_9MgCl" with benzophenone and fluorenone proceeds via a SET pathway while the reaction of "t-C_4H_9MgCl" with acetone appears to follow a polar pathway. The "iron intermediate" proposed to result from the reaction of "CH_3MgBr" with trace amounts of $FeCl_3$ apparently reacts via SET with benzophenone and fluorenone to yield pinacol and yet is apparently unable to transfer an electron to acetone with a reduction potential as high as acetone. In reactions where SET is obviously occurring (such as the reaction of "CH_3MgBr" with benzophenone in the presence of $FeCl_3$ to give a large amount of pinacol), shift to a more polar solvent (e.g., from diethyl ether to THF) results in an observable increase in the proportion of SET products (e.g., pinacol).

The formation of pinacol in the reaction of "CH_3MgBr" with benzophenone has been shown to be the result of a transition metal catalyzed SET reaction. Iron and other first row transition metals appear to be the best catalysts.

The mechanism (eq 1) initially suggested by Blomberg and Mosher and Fauvarque for the reaction of Grignard reagents with ketones is not entirely correct. The reactions of "t-C_4H_9MgCl" with benzophenones and fluorenone apparently

occur via a SET pathway involving a radical anion–radical cation (after SET) which can collapse to give addition products or diffuse to give pinacol and isobutane (eq 21). The reaction of "t-C_4H_9MgCl" with $FeCl_3$ apparently produces an iron hydride species which is capable of reducing acetone more quickly than Grignard addition to acetone but which does not react with benzophenones or fluorenone in the presence of the Grignard reagent.

The reactions of "CH_3MgBr" with ketones are not easily interpreted in terms of the nature of alkyl transfer. They show some of the characteristics of both polar and SET reactions. The main complicating factor is that the reaction of "CH_3MgBr" with $FeCl_3$ (even in trace amounts) produces a species which is capable of SET to each of the ketones tested (except acetone) by an apparently catalytic process involving the Grignard reagent. This electron transfer leads to pinacol in the case of benzophenone or fluorenone. If the mechanism of methyl Grignard reactions with ketones does involve SET, in the absence of transition metal catalysis, to give a radical anion–radical cation pair, collapse of this pair to 1,2-addition product must be extremely rapid and exclusive. No 1,6-addition product or pinacol is ever observed via this pathway.

Grignard reagents have been shown to react with p-dinitrobenzene. However, small amounts of p-DNB in Grignard reactions with ketones have been shown to be capable of inhibiting the formation of "free ketyls" in the solution. Grignard reactions in the presence of p-DNB produce no pinacol in experimental conditions under which it would normally be a product. More important from a mechanistic point of view, reaction of "t-C_4H_9MgCl" with benzophenones in the presence of p-DNB yield no pinacol but give the same ratio of 1,2- to 1,6-addition product as those reactions in the absence of p-DNB. This leads to the conclusion that pinacol and 1,6 addition do not come about through the same intermediate and supports eq 21 as the general mechanism for *tert*-butyl Grignard reactions with ketones. The initially formed radical anion–radical cation pair can collapse to give 1,2 and 1,6 addition or diffuse to yield isobutane and pinacol. Expansion of this idea leads to the postulation of eq 22 as the general mechanism for all Grignard reactions with ketones of sufficiently low reduction potential for SET to take place.

Experimental Section

Materials. Solvents. Fisher reagent grade anhydrous diethyl ether was stored over sodium and then distilled under nitrogen from $LiAlH_4$ and/or sodium benzophenone ketyl just prior to use. Fisher reagent grade tetrahydrofuran, benzene, and 1,2-dimethyoxyethane were dried over $NaAlH_4$ and distilled under nitrogen just prior to use. Fisher reagent grade hexamethylphosphoramide was dried over sodium and distilled under vacuum just prior to use.

Ketones. Eastman highest purity 2-methylbenzophenone and benzophenone were distilled under vacuum. Fisher Certified A.C.S. grade acetone was dried over $MgSO_4$ and then filtered, distilled, and stored over 4A molecular sieves. Eastman highest purity 9-fluorenone was used without further purification. Solutions of these ketones were stored in a glove box and shielded from light prior to use.

Alkyl Halides. Methyl bromide (Matheson 99.5% purity) was dried and purified by passing through a 30-cm tube of NaOH pellets and then through a 70-cm tube of Linde 4A molecular sieve. Fisher reagent grade bromobenzene, *tert*-butyl chloride, and pivaloyl chloride were distilled through an 18-inch glass-helix-packed column.

Transition Metals. $CoCl_3$, CuCl, $CrCl_3$, $FeCl_2$, and $FeCl_3$ (Fisher sublimed) were handled only in the glove box and used without further purification.

Organometallic Compounds. Grignard reagent solutions were prepared as previously described[3] from the following grades of magnesium metal: Baker Grignard grade turnings, Ventron chips (Lot 071173), ROC/RIC crystals, Dow doubly sublimed. The last grade of magnesium was milled with a carbide tool prior to use. The first three grades were used without further milling. Grignard reagents were analyzed by hydrolyzing an aliquot with distilled water, adding excess standard H_2SO_4, and back-titrating with standard NaOH to a phenolphthalein end point. Magnesium was determined by titrating hydrolyzed samples with standard EDTA solution at pH 10 using eriochrome black T as an indicator. In some cases halide was determined by titration with $AgNO_3$ and back-titration by KCNS with ferric alum indicator. In some cases the amount of active CMg was determined by titrating active Grignard reagent with dry 2-butanol in xylene using 2,2′-biquinoline as an indicator. In those cases where all four types of analysis were carried out, the ratio of halide:CMg:Mg:total base was within 3% of 1.0:1.0:1.0:1.0. Grignard reagents in HMPA and THF were prepared by removing the ether from the Grignard reagents under vacuum and adding the appropriate solvent. Grignard reagents in HMPA were used within 1 week of preparation.

Others. Aldrich (99%) 4-*tert*-butylbenzoic acid, and Eastman highest purity p-dinitrobenzene were used without further purification.

Preparations. Miscellaneous. The preparations of 1,1-diphenylethylene and 1,1-diphenylethanol were carried out as previously described.[15] The preparation of acetonepinacol was carried out as previously described.[16]

2,2-Dimethyl-1,1-diphenylpropanol. To a rapidly stirred solution of 0.375 mol of "C_6H_5MgBr" in 300 mL of ether was added 18.5 mL (0.15 mol) of pivaolyl chloride over a period of 60 min. The solution was stirred for 24 h and hydrolyzed with 10% H_2SO_4. The desired product distilled at 116–125 °C (0.5 mm): NMR ($CDCl_3$, TMS) 10 H multiplet at δ 7.2–7.7, 1 H singlet 2.28, 9 H singlet 1.15; single peak by GLC on 2-ft 10% Carbowax 20M column; mass spectrum consistent with structure, M^+ none (240), $M - H_2O$ (222), $M - H_2O$, and methyl (207) and M – *tert*-butyl (183) are characteristic.

4-*tert*-Butylbenzophenone. To a rapidly stirred solution of 0.040 mol of p-*tert*-butylbenzoic acid in 200 mL of ether was added 0.080 mol of "C_6H_5MgBr" in 64.0 mL of ether. The solution was allowed to stir overnight and was hydrolyzed with 10% H_2SO_4. After drying and removing the ether under vacuum, the crude product showed one peak by GLC analysis. After distillation (bp 100–112 °C (0.5 mm)) NMR ($CDCl_3$, TMS) consisted of a 9 H multiplet at δ 7.2–7.7 and a 9 H singlet at 1.38. Mass spectrum was consistent with structure, M^+ 238.

1,1,2,2-Tetramethylpropanol. To 0.40 mol of t-C_4H_9Li in 241 mL of hexane was added slowly 23 mL (0.33 mol) of acetone in 100 mL of hexane. After 4 h the reaction was hydrolyzed. The solvent was removed under vacuum resulting in a viscous liquid. Recrystallization from ether gave a solid: mp 76–79 °C; NMR ($CDCl_3$, TMS) 3 H singlet at δ 0.093, 2 H singlet at 1.18, 1 proton broad singlet at 1.53.

Methods. Apparatus and Procedure. A Varian A-60D MHz spectrometer was used for recording nuclear magnetic resonance spectra. GLC analyses were carried out on F & M Models 700 and 720 gas chromatographs. Materials used in this study were transferred in a glove box described elsewhere[17] or in Schlenk tubes under a blanket of nitrogen.

Calibrated syringes equipped with stainless steel needles were used for transfer of reagents. Ketone and metal salt solutions were prepared by weighing the reagent in a tared volumetric flask and diluting with the appropriate solvent. All metal salt solutions were used within 24 h of preparation. In cases where the metal salt was not ether soluble, a weighed mass was added directly to the Grignard solution immediately prior to the addition of the ketone.

Reactions in General. Glassware and syringes were flamed and taken into a glove box under vacuum. The appropriate amounts of solvent and ketone solutions were syringed into a septum capped flask. An appropriate amount of Grignard reagent was added with swirling. (In some cases the inverse of this addition procedure was used.) In those cases in which the reaction was carried out in the presence of a transition metal salt, the salt was added immediately prior to the addition of the Grignard reagent.

The Grignard reactions with benzophenone and fluorenone typically involved the addition of 1.88 mmol of Grignard reagent to 1.25 mmol of ketone in 10.0 mL of solvent. Higher Grignard to ketone ratios were obtained by increasing the amount of Grignard reagent added and by adding the ketone to the Grignard reagent. Typically, a G/K ratio of 125:1 was obtained by adding 1.0 mmol of ketone to 125 mmol of Grignard reagent in 157 mL of solvent. Reactions were usually allowed to proceed for 4 to 8 h before hydrolysis.

The Grignard reactions with acetone were generally carried out by

mixing 0.28 mmol of Grignard with 0.19 mmol of acetone in 1.5 mL of ether and were usually allowed to proceed for 20 min before hydrolysis with 500–100 μL of saturated NH_4Cl/H_2O. These solutions were dried over $MgSO_4$ before GLC analysis.

The identification of all products from the reaction of "CH_3MgBr" with benzophenone and 2-MBP was made by NMR analysis employing $CDCl_3$ as a solvent and TMS as an internal standard. The products arising from reaction with benzophenone were determined as follows: the 1,2-addition product by the observation of the methyl group attached to the carbinyl carbon (δ 1.92), benzopinacol by the -OH hydrogen (3.05), and benzhydrol by the hydrogen attached to the carbinyl carbon (5.80). The products arising from reaction with 2-MBP were determined as follows: the 1,2-addition product by observation of the methyl group attached to the carbonyl carbon (δ 1.85) and the methyl group bound to the ring (1.96) and 2,2′-dimethylbenzopinacol by observation of the -OH hydrogen (3.16) and the methyl group bound to the ring (2.26). 2,2,3,3-Tetramethylbutane (singlet at δ 0.88) was employed an an internal standard.

The identification of all products from the reaction of "*t*-C_4H_9MgCl" with benzophenone and 2-MBP was made by NMR[18] under nitrogen employing $CDCl_3$ as a solvent and using TMS as an internal standard. The products arising from reaction with benzophenone were determined as follows: the 1,2-addition product by the observation of the *tert*-butyl group attached to the carbonyl carbon (δ 1.15), the 1,6-addition product by the *tert*-butyl group on the ring (0.93 δ), and air oxidation of the 1,6-addition product by the *tert*-butyl group on the ring (1.38). Generally air oxidation was avoided in the workup procedure, but it was shown to be a quantitative conversion when it did occur. Proper analysis is obtained from the total of the two 1,6-addition peaks. The products arising from reaction with 2-MBP were determined as follows: the 1,2-addition product by the *tert*-butyl group attached to the carbonyl carbon (δ 0.98), the 1,6-addition product by the *tert*-butyl group on the ring (0.87), and oxidized 1,6-addition product by the *tert*-butyl group on the ring (1.18). Generally, diphenylmethane was employed as an internal standard (10 H, δ 7.22; 2 H, 4.00). Occasionally, nitromethane (δ 4.32) or acetone (2.13) was employed.

The identification of products of Grignard reactions with fluorenone was made by comparison of the NMR spectra of equivalent products in the benzophenone reactions. The structures of the ketones are very similar and the similarity in the results of the study did not seem to warrant synthesis of authentic samples. Product analysis was determined based on the following assignments: methyl-1,2-addition product by the methyl group on the carbonyl carbon (δ 1.68), *tert*-butyl 1,2-addition product by the *tert*-butyl group on the carbonyl carbon (1.25), *tert*-butyl 1,6-addition product by the *tert*-butyl group on the ring (0.97), oxidized *tert*-butyl 1,6-addition product by the *tert*-butyl group on the ring (1.35), and pinacol by the -OH hydrogens (3.23). The same internal standards were used as with benzophenone.

The identification of all products from the reaction of Grignard reagents with acetone was made by comparison of retention times of authentic samples using GLC on a 12-ft, 20% Carbowax 20M column programmed between 60 and 180 °C (60 °C for 14 min, 130 °C for 14 min, 180 °C for 14 min). An injection port temperature of 220 °C, detector temperature of 300 °C, and a helium flow rate of 60 mL/min were employed. Retention times varied slightly with conditions, but typically they were as follows: acetone, 7.0 min; *tert*-butyl alcohol, 10.1 min; isopropyl alcohol, 12.5 min; 1,1,2,2-tetramethylpropanol, 19.6 min; dodecane, 23.5 min, and pinacol, 36.0 min. Dodecane was employed as internal standard and relative response factors were determined regularly.

In general, reactions involving low Grignard to ketone ratios had essentially 100% material balances. Those reactions involving high Grignard to ketone ratios gave lower material balances (~80%). This is probably due to products being physically removed from the reaction vessel by the large amount of methane produced on hydrolysis. Addition of a dry ice-acetone condensor to the flask prior to hydrolysis improved material balances to nearly 100%.

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