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Organometallic Reaction Mechanisms. 14. Role of Transition Metal Catalysts in the Formation of Aromatic Pinacols and Hydrols during Grignard Reagent Addition to Ketones[1]

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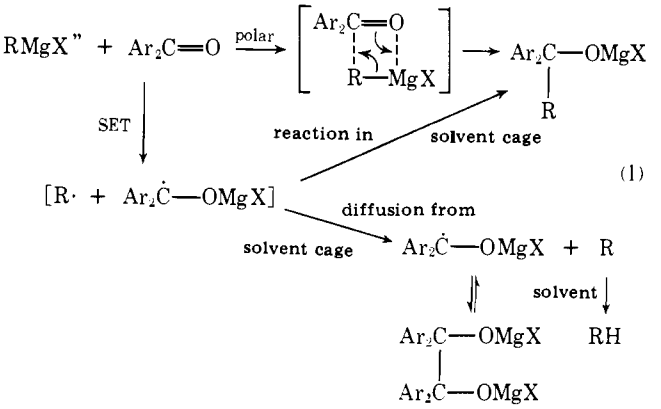
Abstract: The reaction of 2-methylbenzophenone with methylmagnesium bromide was studied under a variety of conditions. Methylmagnesium bromide prepared from magnesium samples containing significant amounts (>20 ppm) of iron and other first-row transition metals yielded substantial amounts of 2,2′-dimethylbenzopinacol at high Grignard to ketone ratios. 2,2′-Dimethylbenzopinacol was also produced in high yield when catalytic amounts of iron and other first-row transition metal salts were added to the Grignard–ketone reaction mixture in nearly equal molar amounts. Multiple regression and correlation analysis shows a direct relationship between the amount of transition metal salt added to the Grignard reagent and the amount of pinacol formed. In reactions with 2-methylbenzophenone, both the erythro and threo pinacols were formed. The threo pinacol (isolated in substantial yield early in the reaction at low temperature) was shown to be the kinetic product which quickly converts to the thermodynamic erythro pinacol (95:5) at room temperature. A mechanism describing the transition metal catalyzed formation of pinacols is presented which is consistent with the known facts about this reaction. The formation of 2-methylbenzhydrol at high Grignard to ketone ratios was found to be due to a minor amount, ca. 0.2%, of a very reactive magnesium hydride species formed during the reaction of methylbromide with magnesium metal in diethyl ether. The relationship between the grade of magnesium used to prepare the Grignard reagent and the amount of 2-methylbenzhydrol formed was found to be due solely to the size of the magnesium crystals and the rate at which methyl bromide was added to the magnesium.

Introduction

The importance of the Grignard reaction in synthetic organic chemistry is well recognized; however, the mechanism whereby Grignard reagents react with organic substrates (and particularly ketones) is not well understood. The exact nature of alkyl transfer from the Grignard reagent to the ketone, whether it proceeds by a polar or a single-electron transfer (SET) mechanism has been a source of considerable speculation. As a result of previous studies,[2] we have discussed in detail the polar mechanism whereby methylmagnesium bromide ("CH_3MgBr") reacts with 2-methylbenzophenone[3] (2-MBP) and benzonitrile.[4] However, while this work was being carried out, evidence was presented by several other research groups to indicate that the reaction of Grignard reagents with ketones could and does proceed in some cases by a SET pathway.

In 1968, Blomberg and Mosher presented evidence supporting SET pathways in Grignard reactions.[5] In the reaction of "neopentylmagnesium chloride" with benzophenone in THF, not only did they observe 1,2 addition, but they also found benzopinacol and neopentane both in 20% yield. Presumably the neopentane arose from hydrogen abstraction of the solvent by a neopentyl radical. In this study, Blomberg and Mosher also reported observing an ESR signal which they assigned to the ketyl. They suggested the mechanism below (eq 1) to explain their data.



(1)

Table I. Products from the Reaction of Methylmagnesium Bromide (1.50 M) with 2-Methylbenzophenone (0.00375 M) in Diethyl Ether at Room Temperature. Effect of Magnesium Purity at 400:1 Grignard to Ketone Ratio

Grade of Mg	Grignard prepared in excess	Yield %				Elemental analysis,[e] ppm											
		1,2 Addition[a]	Pinacol[b]	Hydrol[c]	Other[d]	Ti	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ag	Pb	Na	K
Single crystal	Mg	68	10	13	9	0	0	70	18	0	0.1	3	48	140	0	0.3	0.4
Dow No. 5	Mg	71	7	13	8	17	0	6	18	0	1.0	6	20	0	0	0.3	0.4
Ventron chips	Mg	77	14	0	10	0	0	21	22	0.3	0	0.1	56	0	0	0.3	0
DS[f]	Mg	62	2	36	0	0	0	0	0.1	0	0	0.1	25	0	0	9	0.9
ROC/RIC	Mg	92	1	4	3	0	0	7	10	0	0	0	73	0	18	0	1
TS[g]	Mg	41	1	58	0	0	0	0	0	0.3	0	0	27	0	0	18	16
GGT[h]	Mg	55	19	8	19	0	0	130	140	0	0.1	3	54	0	0	0.3	0
Ventron chips	CH_3Br	85	10	0	5	0	0	21	22	0.3	0	0.1	56	0	0		0
ROC/RIC	CH_3Br	94	4	0	2	0	0	7	10	0	0	0	73	0	18		1
TS[g]	CH_3Br	82	2	4	3	0	0	0	0	0.3	0	0	27	0	0		16

[a] 1-Phenyl-1-(2-methylphenyl)ethanol. [b] 2,2′-Dimethylbenzopinacol. [c] 2-Methylbenzhydrol. [d] Believed to be (2,6-dimethylphenyl)phenylmethylcarbinol. [e] Analysis by Microtrace Analytical Services, Industry, Calif. [f] Doubly sublimed. [g] Triply sublimed. [h] Grignard grade turnings.

Fauvarque has studied the reaction of R_2Mg compounds with fluorenone and benzophenone in various solvents.[6] His ESR observations indicate that ketyl concentration depends on the polarity of the solvent and the ability of the alkyl group to stabilize the radical. Significant amounts of ketyl were observed when dibenzylmagnesium was allowed to react with fluorenone in HMPA; however, the same reaction in ether showed only a trace of ketyl to be present. The proposed SET mechanism is similar to that shown in eq 1.

More recently, Holm and Crossland have presented convincing evidence for a rate-determining SET step in the reaction of "t-C_4H_9MgCl" with benzophenone in diethyl ether.[7] In reactions with various substituted benzophenones, they obtained pinacol, 1,2-, 1,4-, and 1,6-addition product. 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 ortho-methyl groups). In similar reactions using "CH_3MgBr" the presence of only one ortho-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 durylphenyl 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.

While carrying out kinetic experiments which established the first-order dependence of the reaction on the Grignard reagent when "CH_3MgBr" was allowed to react with benzophenone, we made additional important observations.[3,4] We found that the amount of addition product observed compared with by-product (benzopinacol and benzhydrol), as well as the observed rate constant, was dependent upon the ratio of Grignard reagent to ketone, the "purity" of the magnesium used to prepare the Grignard reagent, and the manner in which the Grignard was prepared (that is, using excess magnesium or excess CH_3Br in the preparation).[8] This was interpreted to imply that an impurity-catalyzed side reaction was taking place giving rise to the by-products in the reaction. The exact nature of this side reaction was unknown.

In light of these observations, we have undertaken a detailed study of the reaction of Grignard reagents with benzophenone and 2-MBP. The objective of this study was to determine: (1) the nature of the side reactions giving rise to the by-products, (2) the nature of the impurities catalyzing these side reactions, (3) the extent (if any) of SET pathway operating in Grignard reactions when transition metal catalysts are rigorously excluded, and (4) the conditions which determine the extent of SET reaction.

Results and Discussion

Initial Observations. We observed that when "CH_3MgBr" was allowed to react with 2-MBP in large Grignard:ketone ratios, the product distribution varied widely with both the grade of magnesium and the method of preparation of the Grignard reagent (Table I). While the formation of 2-methylbenzhydrol appears to be dependent mainly on the method of preparation of the Grignard reagent, the amount of 2,2′-dimethylbenzopinacol (2,2′-DMBP) produced appears to depend only on the grade of magnesium used. The "other"[9] product listed in the Table also appears to depend only on the grade of magnesium.

The various grades of magnesium used in these experiments were analyzed by four different methods: spark source mass spectroscopy, emission spectroscopy, proton excited x-ray spectroscopy, and x-ray fluorescence spectroscopy. These methods all gave similar results. Analysis by spark source mass spectroscopy of the transition metal impurities in the various grades of magnesium used in this study are given in Table I. Multiple regression and correlation analysis of the data showed a relationship involving total transition metal content in the magnesium metal and pinacol formation ("correlation coefficient" = 0.905 and "index of determination"[10] = 0.819). The "other" product was shown to have a "correlation coefficient" of 0.967 and an "index of determination" of 0.935. Thus the relationship between the amount of transition metal present in the magnesium metal used to prepare the Grignard reagent and the amount of pinacol and "other" product formed is excellent. On the other hand, the hydrol formed did not correlate at all with the transition metal content of the magnesium. Because the formation of 2,2′-DMBP and that of 2-methylbenzhydrol appear to be quite different in nature, they will be treated in separate sections of this paper.

Mechanism of Pinacol Formation. The formation of pinacols in Grignard reactions with ketones is considered indicative of a SET pathway. The multiple regression and correlation analysis, therefore, points to the existence of a transition metal catalyzed SET pathway in the reaction of "CH_3MgBr" with

Table II. Effect of $FeCl_3$ on the Products from Reaction of "CH_3MgBr"[a] (0.30 M) with 2-Methylbenzophenone (0.030 M) in Et_2O at Room Temperature

		% yield	
$FeCl_3$, mol %	Fe,[b] ppm	1,2 addition[c]	Pinacol[d]
0	0	>99	<1
0.005	115	82	18
0.05	1 148	52	48
0.5	11 362	29	71

[a] Prepared from doubly sublimed magnesium using excess magnesium. [b] Relative to magnesium in "CH_3MgBr". [c] 1-Phenyl-1-(2-methylphenyl)ethanol. [d] 2,2′-Dimethylbenzopinacol.

Table III. Effect of Added Transition Metal Salts (0.5 mol %) in the Reaction of 1.5 mmol of "CH_3MgBr"[a] and 1.0 mmol of 2-Methylbenzophenone in Et_2O at Room Temperature[b]

	% yield		
Metal salt	1,2 addition[c]	Pinacol[d]	2-Methylbenzhydrol
$V(acac)_3$[e]	95	5	0
$Cr(acac)_3$	81	19	0
$Mn(acac)_3$	81	19	0
$MnCl_2$	91	9	0
$Fe(acac)_2$	45	55	0
$Fe(acac)_3$	40	60	0
$FeCl_3$	38	62	0
$Fe(CO)_5$	56	44	0
$Co(acac)_3$	49	51	0
$CoCl_2$	51		49
0			
$Ni(acac)_2$	87	13	0

The salts of the following metals all yielded 100% 1,2 addition: Sr, Y, La, Zr, Hf, Ce, Th, Mo, W, Ru, Rh, Pd, Pt, Cu, Ag, Zn, Cd, Al, Ga, In, Tl, Sn, Pb.

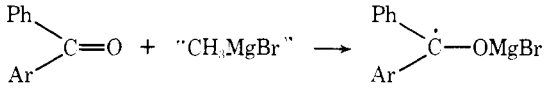
[a] Prepared from doubly sublimed magnesium using excess magnesium. [b] Analysis by NMR. [c] 1-Phenyl-1-(2-methylphenyl)ethanol. [d] 2,2′-Dimethylbenzopinacol. [e] acac = acetylacetonate.

2-MBP. Using $FeCl_3$ as a typical transition metal impurity, we have demonstrated that the relative amount of pinacol found in the reaction products depends on the concentration of iron in the Grignard reagent (Table II). These results lead to the conclusion that the formation of pinacol in the reaction of "CH_3MgBr" with 2-MBP proceeds by a SET pathway and is iron catalyzed. The results prompted closer scrutiny of the work of Holm and Crossland.[7] We felt that possibly the magnesium used in their study contained iron and other transition metal impurities, thus causing the products of SET that they observed. In contrast to our results with "CH_3MgBr", however, we found the product distribution in the reaction of "t-C_4H_9MgCl" with benzophenone is independent of the grade of magnesium used to prepare the Grignard reagent, the method of preparation of the Grignard, and the concentration of transition metal salts added to the Grignard reagent prior to reaction.[11] It is clear then that the reaction of "t-C_4H_9MgCl" with benzophenone proceeds at least partially, if not predominantly, through a SET pathway even in the absence of transition metal impurities.

Once the catalytic effect of iron on reactions of "CH_3MgBr" with benzophenone had been determined, a general study of the effect of transition metal salts was conducted (Table III). Only the first-row transition metals from vanadium to nickel showed any catalytic behavior. Within this series the amount of pinacol formed increased from vanadium through iron then decreased again through nickel. It is interesting to note that, for any given metal, the particular salt or oxidation state of that salt does not seem to be important. Apparently the Grignard reagent is capable of reducing any of the transition metal ions to a common reactive state.[12]

In an effort to find a way to remove the by-product forming impurities in the Grignard reagent, various complexing agents were screened as by-product inhibitors. In the reaction of 1.5 mmol of methylmagnesium bromide with 1.0 mmol of 2-MBP in the presence of 0.05 mol % of $FeCl_3$, addition of 2.0 mol % of ethylenediaminetetraacetic acid disodium salt, triphenylphosphine, 1,10-phenanthroline, 2,2′-biquinoline, tetramethylenediamine, or hexamethylphosphoramide had no effect on the product distribution. In each case the product ratio was about 60% 1,2 addition and 40% 2,2′-DMBP (including the reaction with no added complexing agent).

In order to shed some light on the mechanism of pinacol formation, a study of the role of ketyls in the reaction of "CH_3MgBr" with 2-MBP was carried out. ESR and uv



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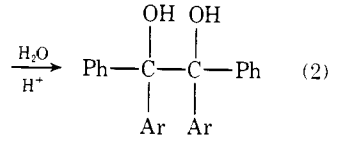


(2)

spectroscopy show that **1** is formed and that a direct relationship exists between the amount of ketyl observed during the reaction and the amount of 2,2′-DMBP found after hydrolysis.[13]

A low-temperature study of the formation of products with respect to time was conducted for the iron-catalyzed reaction of "CH_3MgBr" with 2-MBP (Table IV). Both addition product and pinacol appear in normal fashion and in constant ratio throughout the entire reaction. A comparison of this re-

Table IV. Formation of Products with Respect to Time in the Reaction of "CH_3MgBr"[a] (0.20 M) with 2-Methylbenzophenone (0.020 M) and $FeCl_3$ (0.05 mol %) in Et_2O at −30 °C[b]

		% yield				
			Pinacol[d]			
Rx time	Unreacted ketone, %	1,2 addition[c]	Erythro	Threo	2-Methylbenzhydrol	By-product/addition[e]
40 min	82 (91)[f]	7 (9)[f]	7	4	0	1.5
2 h	47 (85)	21 (15)	19	13	0	1.5
3 h	24 (77)	31 (23)	28	17	0	1.5
4 h	16	31	37	16	0	1.4

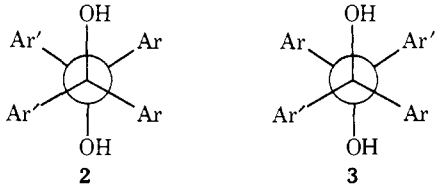
[a] Prepared from doubly sublimed magnesium using excess magnesium. [b] Analysis by NMR. [c] 1-Phenyl-1-(2-Methylphenyl)ethanol. [d] 2,2′-Dimethylbenzopinacol. Composed of both threo and erythro pinacols. [e] (2-Methylbenzhydrol + pinacol)/addition product. [f] Numbers in parenthesis give values for uncatalyzed reaction.

action with the uncatalyzed reaction (parenthetical values, Table IV) shows that the 1,2-addition product was formed at about twice the rate.[14] It appears possible, therefore, that at least some of the 1,2-addition product is being formed through a SET pathway. However, since the catalyzed and uncatalyzed rates are so similar, it does not at all appear clear that true catalysis is taking place. In addition, this result does not allow one to distinguish between two other possibilities: namely, do both the catalyzed and uncatalyzed reactions producing 1,2-addition product proceed by a polar mechanism or do both proceed by a SET mechanism. It does not seem reasonable that the uncatalyzed reaction is proceeding entirely by a polar mechanism and the catalyzed reaction entirely by a SET mechanism since the rates of catalyzed and uncatalyzed reactions are so similar. By the use of probes in both the R group of the Grignard reagent and the substrate, it appears that both the polar and SET mechanisms are competing in this system at least to some extent.[15]

During this low-temperature study, NMR analysis revealed a new product not observed in previous reactions at room temperature. The reaction of 0.20 M "CH_3MgBr" with 0.020 M 2-MBP in the presence of 0.05 mol % of $FeCl_3$ yielded after 7 h at −30 °C, 44% pinacol, 15% addition, and 41% of the new product. However, if the same reaction mixture was allowed to warm to room temperature prior to hydrolysis, 84% pinacol and 16% addition product were obtained. Thus the new product (41%) was converted to the normal pinacol at room temperature. It was also found that when the reaction mixture was held at −30 °C, the new product was very slowly converted to normal pinacol. On the other hand, if the reaction was run at room temperature, 71% pinacol and 20% addition were obtained. If the hydrolyzed reaction mixture containing the new product was recombined with "CH_3MgBr" at room temperature, subsequent hydrolysis provided only pinacol (82%) and addition product (18%).

After removal of the new product and the normal pinacol from the reaction mixture by washing with petroleum ether, the two were separated by column chromatography on silica gel with 10% $CHCl_3$ in petroleum ether. The new product was identified as a diastereomer of the pinacol on the basis of its spectral data (see Experimental Section). Since the "new product" was detected only at low temperature,[16] it is apparently the kinetically formed pinacol. The pinacol normally seen at room temperature is then assigned to be the thermodynamic product.

In hopes of shedding some light on the actual mechanism of formation of the pinacols in the reaction with 2-MBP, it was desirable to determine which of the pinacol diastereomers is the threo form (**2**) and which is the erythro (**3**). Chiral NMR

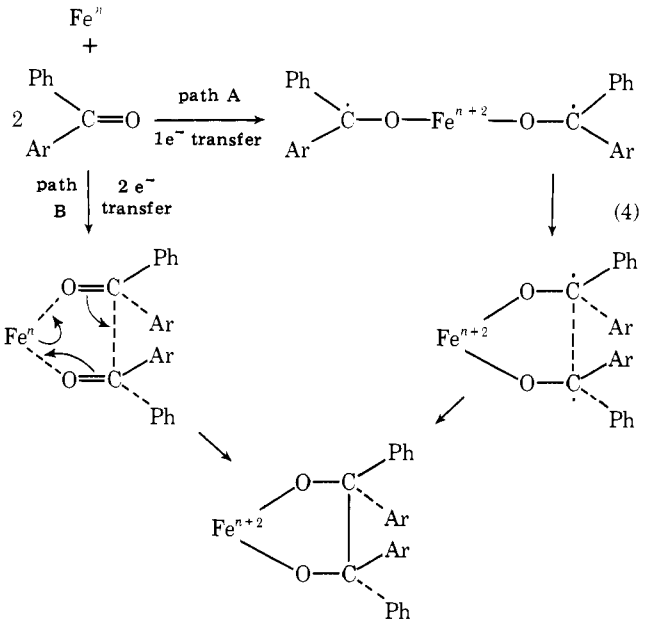


2 **3**

shifts reagents failed to show a splitting of the peaks in the d,l (threo) isomer with a corresponding lack of splitting of the meso (erythro) isomer. These results indicate that the steric crowding around the hydroxyl group is large enough to prohibit any appreciable amount of coordination of either pinacol with the shift reagent. However, since the preferred conformation of the threo form (**2**) has a "cis" glycol arrangement while the erythro (**3**) has trans hydroxyls in the preferred conformation, the threo form (**2**) should react more rapidly with reagents such as lead tetraacetate. When 0.432 mmol of a 2,2′-dimethylbenzopinacol mixture (45% kinetic and 55% thermodynamic product) was allowed to react for 3 days with 0.158 mmol of $Pb(OAc)_4$ (37% of theoretical) in acetic acid at room temperature, NMR analysis after workup showed 55% thermodynamic pinacol, 34% kinetic pinacol, and 11% ketone (30% conversion). Thus, the kinetic isomer reacted preferentially and therefore must be the threo form. The threo pinacol can, of course, achieve a cis-OH conformation more easily than can the erythro isomer since the erythro isomer must bring the two largest groups (2-methylphenyl) together in order to do so.

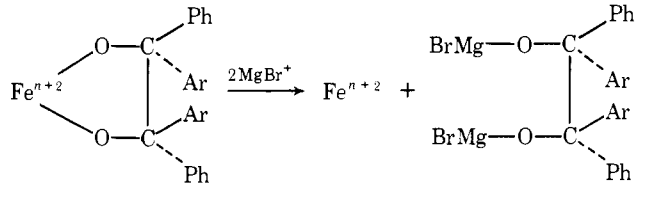
The question arises as to how the threo pinacol is formed and what does its formation as the kinetic product reveal about the mechanism of iron-catalyzed pinacol formation. It seems clear that iron catalysis is involved in the reduction of the ketone to the ketyl. The reduction could be one-electron reduction (path A, eq 4) or a two-electron reduction (path B); however, in either case the threo iron pinacolate would be formed with the larger 2-methylphenyl groups on opposite sides:

$$Fe^{n+2} + 2CH_3MgBr \longrightarrow Fe^{n} + 2CH_3\cdot + 2MgBr^{+} \quad (3)$$



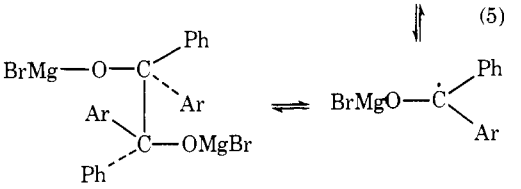
(threo product)

Via either pathway the cyclic iron pinacolate could exchange with magnesium salts to form the bromomagnesium pinacolate followed by dissociation to the free ketyl and recombination to form the thermodynamically more stable erythro isomer:



(kinetic, threo isomer)

(5)



(thermodynamic, erythro isomer)

Our initial efforts to convert the thermodynamic pinacol to the kinetic pinacol at low temperature in excess "CH_3MgBr" (in the presence or absence of $FeCl_3$) were largely unsuccessful, therefore it was necessary to study the kinetic/thermodynamic pinacol equilibrium in detail. At room temperature this equi-

Table V. Kinetic/Thermodynamic Pinacol Equilibrium in the Reaction of "CH_3MgBr" (0.30 M) with 2-Methylbenzophenone (0.025 M) in the Presence of 1.74 mol % $FeCl_3$ at −25 °C

	% pinacol[a]		
Time, h	Kinetic	Thermodynamic	% reaction[b]
~0.08	51.9	48.1	5.8
0.33	51.1	48.9	32.1
1	51.0	49.0	77.1
3	50.0	50.0	85.9
9	45.4	54.6	86.8
24	35.0	65.0	87.9
48	27.3	72.7	90.0
120	28.1	71.9	09.1
241	14.6	85.4	99.3
532	5.1	94.9	100.0

[a] Normalized as % kinetic + % thermodynamic pinacol = 100%. Each reaction contained 2-4% 1,2 addition product as the only other product. [b] 100% − ketone detected in product mixture.

Table VI. Kinetic/Thermodynamic Pinacol Equilibrium Reaction of a 36/64 Mixture of the Diastereomers with "CH_3MgBr" (0.30 M) at −25 °C

	% pinacol[a]	
Time, h	Kinetic	Thermodynamic
0	36.0	64.0
3	36.0	64.0
24	29.9	70.1
120	18.8	81.2
308	4.6	95.4
643	5.3	94.7

[a] Normalized as % kinetic + % thermodynamic pinacol = 100%.

Table VII. Kinetic vs. Thermodynamic Pinacol Equilibrium: Reaction of 97.5/2.5 Mixture of the Diastereomers (0.025 M) with "CH_3MgBr" (0.30 M) at −25 °C with and without $FeCl_3$ (1.74 mol %)

		% pinacol[a]	
Time, h	% $FeCl_3$	Kinetic	Thermodynamic
0	0	2.5	97.5
0	1.74	2.5	97.5
1	0	5.1	94.9
1	1.74	5.1	94.9
4	0	5.0	95.0
4	1.74	5.1	94.9
8	0	5.0	95.0
8	1.74	5.1	94.9
24	0	5.0	95.0
24	1.74	4.9	95.1
48	0	4.8	95.1
48	1.74	5.0	95.0

[a] Normalized as % kinetic + % thermodynamic pinacols = 100%.

librium lies almost entirely (97.5% or more) in favor of the thermodynamic product. At −25 °C, this is also true (95% thermodynamic pinacol). However, at −25 °C, the approach to equilibrium from the side of the kinetic pinacol is very slow (Tables V and VI), whereas approach from the thermodynamic side is faster (Table VII). Furthermore, it appears that the pinacol mixture formed initially in the reaction of "CH_3MgBr" with 2-MBP in the presence of $FeCl_3$ contains approximately equal amounts of kinetic and thermodynamic isomers. Only after the reaction is close to completion does the pinacolate

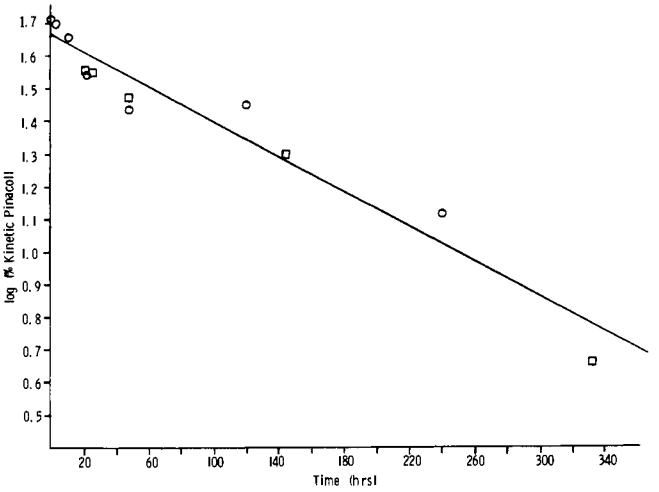
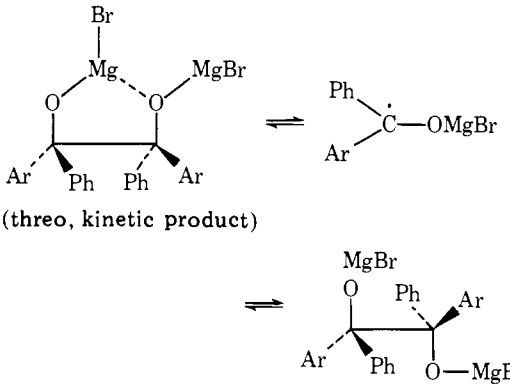


Figure 1. Rate of approach to kinetic vs. thermodynamic pinacol equilibrium with and without added $FeCl_3$. (○) From Table V for the reaction containing Fe; (□) from Table VI for the reaction without Fe. All times are actual time +24 h to simulate equivalent starting ratios of pinacol isomers.

show noticeable equilibration. It also appears that the presence or absence of $FeCl_3$ does not affect the equilibrium or the rate of approach to equilibrium (Figure 1). We feel, therefore, that the equilibrium involved can be simply described by eq 6, and



(threo, kinetic product)

(6)

(erythro, thermodynamic product)

that there is no need to involve iron species in the pinacolate formation step.

These data provide considerable insight into the mechanism of pinacol formation in Grignard reactions with ketones. The indication is that the reduced iron species (eq 3) reduces the ketone to the butyl which then couples indiscriminately with respect to steric effects (eq 6) to give a statistical distribution of threo and erythro pinacolates. With time, equilibrium is established in which the thermodynamically more stable erythro isomer predominates.

The Nature and Mechanism of Hydrol Formation. The production of hydrols in reactions of "CH_3MgBr" with ketones is surprising since methyl Grignard reagents, having no β-hydrogen atoms, would generally not be considered capable of such reductions. Nevertheless, we have shown that when "CH_3MgBr" (prepared from Dow doubly sublimed magnesium) is allowed to react with 2-MBP, 2-methylbenzhydrol is formed, and the amount of this product increases dramatically (Table VIII) as the Grignard:ketone ratio increases. It is important to note that the amount of hydrol produced under a given set of conditions has been shown not only to depend on the grade of magnesium (Table I) used to prepare the Grignard reagent, but also on the particular preparation from the same grade of magnesium. For example, different "CH_3MgBr" solutions, all made from Dow doubly sublimed magnesium

Table VIII. Effect of Grignard to Ketone Ratio on Products from the Reaction of "CH_3MgBr"[a] with 2-Methylbenzophenone in Ether at Room Temperature

["CH_3MgBr"], mol/l.	[2-MBP], mol/l.	["CH_3MgBr"] / [2-MBP]	% yield: Ketone[b]	1,2 addition[c]	Pinacol[d]	Hydrol[e]	[Hydrol[e]], mol/l.
0.010	0.99	1:99	xs	100	0	0	0
0.010	0.11	1:11	xs	100	0	0	0
1.50	1.50	1:1	0	100	0	0	0
1.50	0.15	10:1	0	99	0.6	Tr	Tr
1.50	0.015	100:1	0	89	2	9	0.00135
1.50	0.00375	400:1	0	62	2	36	0.00135
1.50	0.001875	800:1	0	40	4	56	0.00105

[a] Prepared from doubly sublimed magnesium using excess magnesium. [b] 2-Methylbenzophenone [c] 1-Phenyl-1-(2-methylphenyl)ethanol. [d] 2,2′-Dimethylbenzopinacol. [e] 2-Methylbenzhydrol.

Table IX. Formation of Products with Respect to Time in the Reaction of "CH_3MgBr"[a] (0.50 M) with 2-Methylbenzophenone (0.00125 M) in Et_2O at −30 °C[b]

Rx time	Unreacted ketone, %	% yield: 1,2 addition[c]	Pinacol[d]	2-Methylbenzhydrol	Hydrol/addition
10 s	68	2.7	1.7	28	10.4
1 h	46	18	2.0	34	1.9
4 h	10	48	2.3	39	0.81
12 h	0	56	2.5	41	0.73

[a] Prepared from doubly sublimed magnesium using excess magnesium. [b] Analysis by NMR. [c] 1-Phenyl-1-(2-methylphenyl)ethanol. [d] 2,2′-Dimethylbenzopinacol.

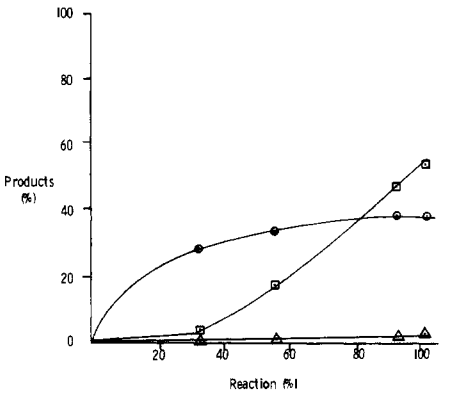


Figure 2. % product vs. % reaction in the reaction of "CH_3MgBr" (0.50 M) with 2-MBP (0.00125 M) in Et_2O at −30 °C. (○) 2-Methylbenzhydrol; (□) 1-phenyl-1-(2-methylphenyl)ethanol; (△) 2,2′-dimethylbenzopinacol.

using excess magnesium, when allowed to react with 2-MBP, formed 2-methylbenzhydrol in yields varying from 36 to 72%. However, duplicate runs from the same Grignard solution are reproducible to within 3%. It has also been shown (Table I) that preparation of the "CH_3MgBr" from excess methyl bromide greatly decreases the ability of the Grignard to reduce benzophenone.

It is also important to note (Table VIII) that when a constant amount of "CH_3MgBr" is allowed to react with decreasing amounts of ketone, the relative amount of 2-methylbenzhydrol produced increases with respect to the initial concentration of ketone; however, the absolute amount of hydrol remains constant (this observation has also been made by Rudolph and Smith[17]). These data indicate that the agent which produces the hydrol is used up stoichiometrically in the reaction. A low-temperature product study makes this point dramatically (Table IX, Figure 2). For example, when "CH_3MgBr" (0.05 M) was allowed to react with 2-MBP (0.00125 M) at −30 °C and samples taken with time, the data clearly show that more than one reaction pathway is in operation and that initially the ketone is rapidly reduced to the hydrol before 1,2 addition becomes significant. From these observations, it is clear that the hydrol must be caused by some "impurity" (estimated 0.1–0.2%)[18] in the Grignard reagent.

$$\text{"}CH_3MgBr\text{"} + Ph_2C{=}O \rightarrow Ph_2\dot{C}\text{-}OMgBr$$
$$\rightarrow Ph_2\ddot{C}\text{-}OMgBr \xrightarrow[H^+]{H_2O} Ph_2CHOH \quad (7)$$

$$\text{"}CH_3MgBr\text{"} + Ph_2C{=}O \rightarrow [CH_2{:} + HMgBr]$$
$$\overset{H}{\rightarrow} Ph_2C\text{-}OMgBr \xrightarrow[H^+]{H_2O} Ph_2CHOH \quad (8)$$

$$Ph_2\dot{C}\text{-}OMgBr + (CH_3CH_2)_2O$$
$$\overset{H}{\rightarrow} Ph_2C\text{-}OMgBr \xrightarrow[H^+]{H_2O} Ph_2CHOH \quad (9)$$

$$Ph_2\ddot{C}\text{-}OMgBr + (CH_3CH_2)_2O$$
$$\overset{H}{\rightarrow} Ph_2C\text{-}OMgBr \xrightarrow[H^+]{H_2O} Ph_2CHOH \quad (10)$$

$$[M\text{-}H] + Ph_2C{=}O \rightarrow \overset{H}{Ph_2C}\text{-}OM \xrightarrow[H^+]{H_2O} Ph_2CHOH \quad (11)$$

A number of pathways appear possible to explain the formation of hydrol (eq 7–11). An investigation into these possibilities was carried out. When "CH_3MgBr" was allowed to react with 2-MBP in 400:1 ratio and the reaction mixture quenched with 99.9% D_2O, no deuterium incorporation at the α-carbon was observed, indicating that the hydrol is not a result of dianion formation followed by hydrolysis (eq 7). Also when "CD_3MgBr" was allowed to react with 2-MBP, no deuterium incorporation at the α-carbon was observed, indicating the

Table X. Formation of 2-Methylbenzhydrol at 400:1 Grignard to Ketone Ratio

Grignard[a] formed in	Reaction carried out in	% yield reduction product[b] $C_6H_5(C_7H_7)CHOH$	% yield reduction product[b] $C_6H_5(C_7H_7)CDOH$
$(CH_3CH_2)_2O$	$(CH_3CH_2)_2O$	59	
$(CH_3CD_2)_2O$	$(CH_3CD_2)_2O$	0	27
$(CH_3CH_2)_2O$	$(CH_3CD_2)_2O$	65	0

[a] CH_3MgBr prepared from Dow doubly sublimed magnesium. [b] Normalized as % 1,2 addition + % reduction = 100%.

Table XI. Selectivity of Reduction of an Equimolar Mixture of 2-Methylbenzophenone and Acetone with "CH_3MgBr" and "CH_3MgBr" + MgH_2[a]

Grade of magnesium used to prepare "CH_3MgBr"	1,2 addition[b] products, %	Reduction products, %[b] 2-Methylbenzhydrol	Reduction products, %[b] Isopropanol
Dow (DS)	74.5	25.0	0.5
ROC/RIC[c]	100.0	0	0
ROC/RIC[c] + MgH_2	74.0	24.5	1.5

[a] Millimoles of each ketone = 0.3; mmol of CH_3MgBr = 120; mmol of MgH_2 = 0.2. [b] Yields normalized as % 1,2 addition + % reduction = 100%. [c] Grignard prepared in excess CH_3Br.

absence of a reaction as described by eq 8. In a series of experiments the bromomagnesium ketyl was formed by the reaction of "CH_3MgBr" with 2,2′-DMBP in 2:1 ratio and the resulting solution altered in ways that produce a solution similar to what exists in the reaction mixture involving the reaction of "CH_3MgBr" with 2-MBP. In the presence of Grignard:ketyl ratios ranging from 1 to 800, $FeCl_3$ ranging from 0.0 to 0.5 mol %, and 1,2-addition product ranging from 0.0 to 1.0 equiv, the ketyl, upon hydrolysis, yielded only 2,2′-DMBP. In no case was any 2-methylbenzhydrol detected. These results indicate that neither the ketyl nor the dianion (possibly formed by the reaction of ketyl in excess Grignard reagent with iron catalysis, eq 9 and 10) can account for the formation of hydrol in the reaction of "CH_3MgBr" with 2-MBP.

In a separate series of reactions, "CH_3MgBr" was allowed to react with 2-MBP in $(CH_3CD_2)_2O$ (Table X). An intermediate ketyl may be expected to abstract D· from the α position of the solvent while the dianion would be more likely to abstract H^+ from the β position. When "CH_3MgBr" was prepared in $(CH_3CD_2)_2O$ and the reaction with ketone carried out in the same solvent, all of the hydrol formed contained D on the α-carbon [$C_6H_5(C_7H_7)C(D)OH$]. This result shows that the hydrogen used in the reduction comes from the ether and also provides further evidence that the dianion (eq 10) is not an intermediate. However, when "CH_3MgBr" prepared in $(CH_3CH_2)_2O$ was desolvated and redissolved in $(CH_3CD_2)_2O$ and the resulting solution allowed to react with 2-MBP, all of the hydrol produced was $C_6H_5(C_7H_7)C(H)OH$. This result demonstrates that the hydrogen abstraction from the ether does not take place when "CH_3MgBr" reacts with the ketone, but during the formation of the "CH_3MgBr". These data strongly indicate once again that the pathways described by eq 9 and 10 are not in effect. It appears that the hydrol producing species must be formed during the Grignard preparation step and that this species is much more highly reactive as a reducing agent toward ketones than is the Grignard reagent as an alkylating agent (Figure 2). These experiments also indicate that the step involving the formation of the reducing species is radical in nature (since the α-D was abstracted from the ether in spite of the primary deuterium kinetic isotope effect involved.)

Since analysis of Dow doubly sublimed magnesium[19] shows no trace element or combination of trace elements in sufficient quantity (~0.2%) to account for the amount of reducing agent necessary to form benzhydrol in up to 72% yield, it seems that the active reducing agent must be a magnesium hydride species. Although a magnesium hydride species has never before been reported as a by-product in the formation of a Grignard reagent, we have carried out several experiments which demonstrate that indeed this is the case. Table XI illustrates the striking similarity in reduction selectivity between an equimolar mixture of 2-MBP and acetone with "CH_3MgBr" prepared from Dow doubly sublimed magnesium and reduction of the same mixture with "CH_3MgBr" prepared from ROC/RIC magnesium crystals (which gave no reduction of 2-MBP) with added MgH_2. In both cases the reduction product is almost exclusively 2-methylbenzhydrol (98% vs. 94%). The fact that considerable reduction is observed in such a large excess of alkylating agent (500:1) indicates that MgH_2 dissolved in Grignard reagent is an unusually powerful reducing agent toward ketones.

Further evidence that MgH_2 in the Grignard reagent is the source of the observed reduction is indicated by the similarity in observed stereochemistry when "CH_3MgBr" that gives reduction (Grignard prepared from Dow doubly sublimed magnesium) reduces 4-*tert*-butylcyclohexanone compared with "CH_3MgBr" that normally does not give reduction (Grignard prepared from ROC/RIC magnesium) except when MgH_2 is added to the reagent. The data in Table XII show that the reduction of "CH_3MgBr" (Dow doubly sublimed) with 4-*tert*-butylcyclohexanone yields the reduction product in 89:11 ratio (equatorial:axial alcohol). On the other hand, "CH_3MgBr" prepared from ROC/RIC magnesium which normally does not give any reduction product, produces a 79:21 ratio of alcohols (equatorial:axial) when MgH_2 is added. The similarity of the above stereochemistry is even more striking when compared with MgH_2 alone, which gives a 32:68 ratio of reduction products.

A number of studies have indicated that Grignard formation is a radical process.[20] From our data it is apparent that up to

Table XII. Stereochemistry of Reduction of 4-*tert*-Butylcyclohexanone (0.3 mmol) with "CH_3MgBr" (120 mmol) and "CH_3MgBr" + MgH_2

Grade Mg used	mmoles of MgH_2	Alkylation, % Total[a]	Alkylation, % Axial[b] alcohol	Alkylation, % Equatorial[b] alcohol	Reduction, % Total[a]	Reduction, % Axial[b] alcohol	Reduction, % Equatorial[b] alcohol
Dow (DS)	0	84	66	34	16	11	89
ROC/RIC[c]	0	100	59	41	0		
ROC/RIC[c]	0.2	92	62	38	8	21	79
	0.3				100	68	32

[a] Normalized as − % alkylation alcohols + % reduction alcohols = 100%. [b] Normalized as − % axial alcohol + equatorial alcohol = 100%. [c] Grignard prepared in excess CH_3Br.

Table XIII. Effect of the Size of Magnesium Shavings and Methyl Bromide Flow Rate on the Percentage of 2-Methylbenzhydrol Formed in Reactions Involving 1.5 M Methylmagnesium Bromide[a] with 0.00375 M 2-Methylbenzophenone

Mg shaving size	Flow rate, cm/min	% yield[b] 1,2 addition	Pinacol	Hydrol
Fine	214[c]	41	ND	59
Fine	682[d]	74	ND	27
Medium	682[d]	84	ND	16
Large	682[d]	91	ND	9

[a] All preparations utilized 28 g of Dow doubly sublimed magnesium. [b] Normalized as − % 2-methylbenzhydrol + % 1,2 addition = 100%. [c] Flow time = 85 min. [d] Flow time = 28 min.

0.2% of a radical species must react with ether to form an active hydride species. The following reaction is suggested:

$$CH_3CH_2OCH_2CH_3 + [\cdot MgBr] \rightarrow [HMgBr] + CH_3CHOCH_2CH_3 \quad (12)$$

It was not initially apparent, though, why "CH_3MgBr" prepared from some grades of magnesium led to more hydrol than those samples prepared from other grades under the same reaction conditions (Table I). Qualitatively it was noticed that the Grignard reagents prepared from large magnesium chips (Ventron chips and ROC/RIC crystals) gave little benzhydrol, while intermediate size chips (Grignard grade turnings and Dow No. 5) led to intermediate amounts of benzhydrol, and finally those prepared from fine shavings (Dow doubly and triply sublimed) gave the most benzhydrol. A glance at Table I clearly indicates that much less hydrol formation is observed when the "CH_3MgBr" is prepared in excess methyl bromide. Thus it appears that the CH_3Br is destroying the active hydride species during Grignard reagent formation. In order to test this point, 2-MBP (0.3 mmol) was allowed to react with "CH_3MgBr" (120 mmol, ROC/RIC crystals) to which 0.2 mmol of MgH_2 had been added. The resulting product mixture contained 79% 2-methylbenzhydrol. The same reaction was carried out after addition of six drops of methyl bromide to the Grignard reagent before addition of the Grignard reagent to the ketone. The resulting product mixture contained only 15% 2-methylbenzhydrol. Similar experiments were carried out using the "CH_3MgBr" prepared from Dow doubly sublimed magnesium (no MgH_2 added) with similar results. It is clear, then, that methyl bromide is capable to destroying the activity of both the dissolved magnesium hydride species that is formed in the preparation of the Grignard reagent as well as that added as MgH_2.

The size of the magnesium chips used in the Grignard preparation has a direct bearing on the amount of CH_3Br that builds up in the reaction mixture. Large magnesium chips have a relatively small surface area which allows CH_3Br to build up during the formation of the Grignard reagent, thereby destroying the magnesium hydride species. On the other hand, a much more finely divided grade of magnesium metal would be expected to react with CH_3Br much more rapidly than the larger magnesium chips thus avoiding a build up of CH_3Br in solution. Thus it is expected that the latter finely divided magnesium would produce a Grignard reagent that contains more hydride and hence would result in more reduction. It is also probable that the rate of addition of CH_3Br during the preparation of "CH_3MgBr" would have an important effect on the hydride content of the resulting Grignard reagent. A rapid flow of CH_3Br would tend to cause Grignard reagent of low hydride content, and slow CH_3Br addition would tend to form Grignard reagents of high hydride content. In the preparations of "CH_3MgBr" for this study, no attempt was made to quantitatively control CH_3Br flow rates. The general procedure was to set the methyl bromide flow rate such that gentle ether reflux was maintained during Grignard formation. This, of course, necessitated the use of higher flow rates when forming "CH_3MgBr" from larger magnesium chips to maintain the same apparent rate of reaction.

In order to investigate the effect of the size of magnesium shavings used to prepare the Grignard reagent and the effect of methyl bromide flow rate, the following experiments were carried out. A block of Dow doubly sublimed magnesium was carefully milled with a new carbide tool to obtain fine shavings (approximately normal size for the Dow doubly sublimed magnesium we had been using), medium shavings (approximately Grignard grade turnings in size), and large chips (approximately ROC/RIC crystals in size). Methylmagnesium bromide was prepared from magnesium shavings of each size at a constant flow rate of 214 and 682 ml min^{-1} (Table XIII). The slower flow rate was set such that gentle ether reflux was maintained in preparation of "CH_3MgBr" employing the fine shavings (i.e., a condition intended to maximize 2-methylbenzhydrol formation). The mass of magnesium was the same to within 0.1 g in all three preparations, and the flow time was cut by one-third at the higher flow rate such that the total amount of CH_3Br added was the same in all six preparations. The implications are clear. The percentage of 2-methylbenzhydrol found in the reactions decreases in a regular way at constant CH_3Br flow rate as the size of the magnesium shavings are increased and as the CH_3Br flow rate is increased. Thus the importance of excess CH_3Br during the preparation of the Grignard is very important in determining the amount of MgH_2 remaining in the Grignard reagent after its preparation.

General Conclusions

The mechanism (Scheme I) initially suggested by Blomberg-Mosher and Fauvarque for the reaction of Grignard reagents with ketones appears to be basically correct. 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 isolation of erythro and threo pinacols in addition to equilibrium studies relating rates of formation of the two isomers show that although iron salts catalyze electron transfer to form the ketyl, iron is not involved in the formation of the pinacols.

The formation of "CH_3MgBr" from magnesium and methyl bromide in ether has been shown to be accompanied by the formation of about 0.2% of a very reactive magnesium hydride species. This hydride has been shown to be responsible for the formation of benzhydrol in reactions of benzophenones using a large excess of "CH_3MgBr". Excess methyl bromide has been shown to destroy the activity of this hydride.

Experimental Section

Methylmagnesium bromide solutions were prepared as previously described.[3] Magnesium was milled with a carbide tool prior to use. Analysis showed the ratio C-Mg:Mg:total base was within 3% of 1.0:1.0:1.0.

The preparations of 1-(2-methylphenyl)-1-phenylethylene and 1-(2-methylphenyl)-1-phenylethanol were carried out as previously described.[21] The preparation of active magnesium hydride has also been previously described.[22]

Preparations. Preparation of 2-Methylbenzhydrol. 2-Methylbenzophenone (5.88 g, 30 mmol) was reduced with 15 mmol of $LiAlH_4$ in THF/Et_2O at 0 °C. After 3.5 h at room temperature, the reaction was hydrolyzed with aqueous NH_4Cl and dilute HCl. The ether layer

was washed with aqueous $NaHCO_3$, dried with $MgSO_4$, and the ether removed under vacuum. The crude solid was recrystallized from hexane: mp 89.5–90.5 °C; ir (neat between plates) 3.1 (broad), 3.2–3.4 (multiplet), 6.25, 6.3, 6.7, 6.85, 6.9 μ; NMR ($CDCl_3$, Me_4Si) 2.26 (3 H, singlet), 2.25 (broad, 1 H, Singlet), 6.05 (1 H, singlet), 7.12–7.73 ppm (9 H, multiplet).

Preparation of 2,2′-Dimethylbenzopinacol. Methylmagnesium bromide (12 mmol) containing 2 mol % of $FeCl_3$ was added to 10 mmol of 2-methylbenzophenone in 20 ml of diethyl ether. After 2.5 h the reaction was hydrolyzed with aqueous NH_4Cl, the ether layer was dried with $MgSO_4$, and the ether was removed under vacuum. The crude product was recrystallized from $CHCl_3$ at 0 °C, washed with petroleum ether and air dried: mp 151–153 °C; NMR ($CDCl_3$, Me_4Si) 1.98 (6 H, singlet), 3.16 (2 H, singlet, sharp), 6.60–7.42 (16 H, multiplet), 7.90–8.16 ppm (2 H, multiplet).

Preparation of CH_3CD_2OH. *n*-Butylacetate (142 g, 1.22 mol) in 100 ml of diethyl ether was reduced by slowly adding 0.65 mol of $LiAlD_4$ in 900 ml of diethyl ether. After addition of $LiAlD_4$ solution was complete, the reaction mixture was allowed to reflux for 2.5 h, then slowly hydrolyzed with 200 ml of distilled water. The ether layer was decanted, dried over anhydrous $MgSO_4$, and filtered. The ether was removed by distillation through a 2-ft packed column. This procedure was repeated and the batches were combined. Fractional distillation yielded 94.1 g (1.96 mol) of CH_3CD_2OH.

Preparation of CH_3CD_2Br. CH_3CD_2OH (1 mol) was added dropwise at 0 °C to a 500-ml round-bottomed flask containing 200 g of 48% HBr and 30 ml of concentrated H_2SO_4. After all CH_3CD_2OH had been added, 51 ml of concentrated H_2SO_4 was added dropwise at room temperature. The reaction mixture was heated on an oil bath and the fraction boiling at 35–38 °C was collected. The CH_3CD_2Br was washed with 10% Na_2CO_3 and dried over $MgSO_4$ (yield 96.3 g, 0.868 mol).

Preparation of CH_3CD_2ONa. CH_3CD_2OH (0.96 mol) in 50 ml of dimethoxyethane was added dropwise at 0 °C to 49.8 g (1.18 mol) of NaH in 400 ml of dry dimethoxyethane with vigorous stirring. After addition of CH_3CD_2OH was complete the reaction mixture was stirred for 19 h at room temperature.

Preparation of $(CH_3CD_2)_2O$. To the CH_3CD_2ONa, 0.8 mol of CH_3CDBr in 50 ml of dimethoxyethane was added slowly. The reaction mixture was stirred at room temperature for 17 h, followed by heating to 40 °C for 7 h, followed by stirring at room temperature overnight. The $(CH_3CD_2)_2O$ (22.5 g) was isolated by fractional distillation (bp 34.5–35.5 °C). NMR analysis (singlet, 1.17 ppm) indicated the $(CH_3CD_2)_2O$ to be essentially 100% isotopically pure.

Apparatus and Procedure. Materials used in this study were transferred in a glovebox described elsewhere[23] 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 diethyl ether. 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. The solution of "CH_3MgBr" + active MgH_2[24] was prepared by placing 25 mmol of MgH_2 in a 250-ml flask under N_2 flush and adding 50.42 ml of 2.38 M "CH_3MgBr" (prepared from ROC/RIC magnesium, 120 mmol).

Reactions in General. Glassware and syringes were flamed and taken into a glovebox under vacuum. The appropriate amounts of diethyl ether and "CH_3MgBr" solutions were syringed into a septum capped flask. An appropriate amount of ketone solution was added with swirling. 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 addition of ketone. When low temperatures were required, the capped flask was removed from the drybox and immersed in a bath at the appropriate temperature before addition of the ketone. After complete reaction the mixture was hydrolyzed with saturated aqueous NH_4Cl solution under a nitrogen atmosphere. The ether layer was separated, dried over anhydrous $MgSO_4$, filtered, and the solvent removed under vacuum.

Low Grignard to ketone ratio reactions typically involved addition of 0.625 mmol of ketone to 0.9 mmol of "CH_3MgBr" in a total volume of 5 ml of ether. The high Grignard to ketone ratio reactions generally involved addition of 0.3 mmol of ketone to 120 mmol of "CH_3MgBr" in a total volume of 80 ml of ether. Reactions were usually allowed to proceed for 4 h before hydrolysis.

Product Analysis in General. The identification of all products from the reaction of "CH_3MgBr" with benzophenone and 2-methylbenzophenone was determined by NMR analysis employing $CDCl_3$ as a solvent with internal Me_4Si. For the products arising from reaction with benzophenone: 1,2 addition was determined by the observation of the methyl group attached to the carbonyl carbon (1.92 ppm), benzopinacol was determined by the -OH hydrogen (3.05 ppm), and benzhydrol was determined by the hydrogen attached to the carbonyl carbon (5.80 ppm). For the products arising from reaction with 2-MBP: 1,2 addition was determined by observation of the methyl group attached to the carbonyl carbon (1.85 ppm) and the methyl group bound to the ring (1.96 ppm), and 2,2′ DMBP was determined by observation of the -OH hydrogen (3.16 ppm) and the methyl group bound to the ring (2.26 ppm). 2,2,3,3-Tetramethylbutane (singlet, 0.88 ppm) was employed as an internal standard and material balances were 100% when a dry ice–acetone condensor was used.

Products vs. Time Studies. The Grignard reactions were run in a special kinetics flask which consisted of a 100-ml round-bottomed flask fitted with a septum cap and placed in a dry ice–CCl_4 bath. A two-way Teflon stopcock was attached near the bottom of the flask (through the back) at such an angle as to allow magnetic stirring. When a sample was desired, the flask was pressurized with nitrogen and the stopcock opened briefly to allow the appropriate amount of sample to be forced into a saturated aqueous NH_4Cl solution cooled to 0 °C (vigorously stirred). A fast flush of nitrogen was directed along the stopcock delivery tube to further reduce any contact with the air prior to hydrolysis. The hydrolyzed aliquots were worked up and analyzed in the usual fashion.

Reactions in Deuterated Ethers. The reaction using "CH_3MgBr" prepared in $(CH_3CD_2)_2O$ and allowed to react with ketone in $(CH_3CD_2)_2O$ was carried out in the usual fashion. In the reaction of "CH_3MgBr" prepared in $(CH_3CH_2)_2O$ and allowed to react with the ketone in $(CH_3CD_2)_2O$, it was necessary to remove the protio ether under vacuum and heat the resulting solid for 4 h at 100 °C before adding the deuterio ether. The reaction with ketone was then carried out as usual.

Reactions Showing the Selectivity of the Magnesium Hydride Reducing Species. To an ether solution containing 120 mmol of "CH_3MgBr" or "CH_3MgBr" + MgH_2"[22] was added 0.3 mmol of 2-MBP and 0.3 mmol of acetone. Reactions were carried out for 4 h, and hydrolysis was followed by vacuum stripping of the volatile portion. Analysis of this portion was obtained by GLC on a 19-ft, 15% diglycerol on 60/80 mesh Chromasorb W column at 60 °C and a flow rate of 60 ml/min of helium using 3,3,5-trimethylcyclohexanone as an internal standard. The retention times for the *tert*-butanol (addition product) and the *i*-propanol (reduction product) were 12 and 15 min, respectively. Extraction of the residue after vacuum stripping gave the rest of the reaction products which were then analyzed in the normal manner.

Reaction Showing the Stereochemistry of Reduction of 4-*tert*-Butylcyclohexanone by the Magnesium Hydride Species. These reactions were carried out in the normal manner. Analysis was carried out by GLC using 10% FFAP on Diatoport S on a 20-ft column at 150 °C with a flow rate of 20 ml/min of helium using 3,3,5-trimethylcyclohexanone as the internal standard. The retention times are as follows: axial alcohol, 39.5 min and equatorial alcohol, 47 min, and the addition products: axial alcohol, 20 min and equatorial alcohol, 34 min. All retention times were determined by comparison with authentic compounds.

Formation, Separation, and Identification of *threo*- and *erythro*-2,2′-Dimethylbenzopinacol. A mixture (roughly 50:50) of the two pinacols was prepared by reacting 25 mmol of CH_3MgBr with 5.0 mol of 2-MBP and 0.125 mol (0.5 mol %) of $FeCl_3$ at −30 °C. After 4 h, the reaction was hydrolyzed with aqueous NH_4Cl at −30 °C. Normal workup followed by washing the crude solid with petroleum ether gave a mixture of the two pinacols.

The pinacols were separated by column chromatography on silica gel, eluting first with 10% CH_2Cl_2 in petroleum ether. The "normal" thermodynamic pinacol washed off of the column first, followed closely by the kinetic one.

NMR: ($CDCl_3$, Me_4Si) (thermodynamic) 1.98 ppm (6 H, singlet), 7.90–8.16 ppm (2 H, multiplet); (kinetic) 1.82 ppm (6 H, singlet), 3.23 ppm (2 H, singlet, broad), 6.84–7.66 ppm (18 H, multiplet). Ir: (thermodynamic) 2.80 (broad), 3.25–3.44 μ; (kinetic) 2.78 (broad), 3.27 and 3.37 μ, fingerprint region very similar to the other pinacol.

Uv	λ_{max}	E
Thermodynamic	225	1200
Kinetic	254	1400

$Pb(OAc)_4$ Oxidation of *threo*- and *erythro*-2,2'-Dimethylbenzopinacol. 2,2'-Dimethylbenzopinacol (0.432 mol) (55% thermodynamic, 45% kinetic) was allowed to react at room temperature with 0.158 mol of $Pb(OAc)_4$ in 10 ml of acetic acid for 3 days. After hydrolysis and normal workup, NMR analysis showed 34% kinetic, 55% thermodynamic, and 11% ketone (30% complete reaction).

References and Notes

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Oxygen Activation by Transition Metal Complexes. 2. Bis(acetylacetonato)cobalt(II)-Catalyzed Oxidation of Tributylphosphine[1]

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Abstract: The oxidation of Bu_3P (**1**), catalyzed by $Co(acac)_2$ (**2**) is described. In MeCN under air at 0 °C the catalyzed oxidation of **1** gives mainly Bu_3PO, but $(BuO)Bu_2PO$ also forms in 20–30% yield, along with smaller amounts of other products. If Ph_2NH, or one of several other free-radical inhibitors, is added to the system, the oxidation proceeds rapidly and gives Bu_3PO as the *exclusive* product. Under these conditions the reaction is first order in cobalt species, one-half order in oxygen, and zero order in Bu_3P. However, spectroscopic studies showed that in solution most (≥80%) of the cobalt is present as $[(Bu_3P)Co(acac)_2]$ (**8**). The formation constant for **8** was estimated at room temperature to be $40 \pm 10\ M^{-1}$; thus the rate law for the reaction is given by rate $= k[(Bu_3P)Co(acac)_2][O_2]^{1/2}$. Complex **2** also catalyzed the oxidation of (*R*)-(−)-MePhPrP (**9**) to (*S*)-(−)-MePhPrPO with *retention* of configuration, as well as a slower conversion of $(BuO)_3P$ to $(BuO)_3PO$, but Ph_3P and $(PhO)_3P$ failed to undergo oxidation. By observing the catalytic activity of a number of other cobalt complexes, the importance of open coordination sites, as well as the redox potential of the complex, was noted. A mechanism is proposed to account for these results (Scheme I). It involves the reaction of **8** with O_2 to give a binuclear μ-peroxide **11**; the *reversible* dissociation of **11** via homolysis of the central O–O bond to give $[(Bu_3P)(acac)_2CoO]$ **12**; and the intramolecular rearrangement of **12** to give $[(Bu_3PO)Co(acac)_2]$ (**13**) in the product-forming step. The relationship of this reaction and mechanism to other metal-catalyzed oxygenations is discussed.

Under ordinary conditions most organic compounds are kinetically unreactive toward molecular oxygen. The major reasons for this lie in the properties of the oxygen molecule itself. Since oxygen has a triplet ground state, its direct combination with singlet organic molecules is a spin-forbidden process. Transition metals and their ions having multiple spin and oxidation states of suitable energy are not subject to the above restriction and can readily interact with the oxygen molecule, even to the extent of forming isolable oxygen adducts. In the complexed form the properties of the oxygen molecule are altered and the changes are often manifested as an increased reactivity of coordinated oxygen toward organic compounds. For example, π complexes of oxygen with d^6, d^8, and d^{10} metal centers are diamagnetic and catalyze several characteristic oxidations of organic phosphines,[2-5] isocyanides,[3] and olefins[5-7] by mechanisms which have been characterized as intracomplex rearrangements leading to the four-electron reduction of coordinated O_2 by two ligand molecules. On the other hand metal–superoxide complexes containing a paramagnetic Co(III)–O–O· moiety are free radical-like and are well known to react by one-electron steps or hydrogen abstractions. Thus these oxygen complexes catalyze the oxidation[8-10] or oxidative coupling[10,11] of phenols and thiols.[12] Metal–superoxide complexes are also intermediates in the