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NEW METHODOLOGY IN DETERMINING EVIDENCE FOR SINGLE ELECTRON TRANSFER IN THE REACTION OF GRIGNARD REAGENTS WITH KETONES *

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Summary

A new method is reported to determine the existence of single electron transfer in the reaction of Grignard reagents with ketones. The method involves the determination of pseudo-first order rate constants by following the rate of disappearance of the paramagnetic intermediate and relating the rate of this disappearance to the appearance of product. The reactions of methyl-, phenyl- and t-butyl-Grignard reagents with substituted benzophenones were examined. This method should be applicable to a wide range of organometallic reactions.

Introduction

The importance of Grignard reagents in synthetic organic chemistry is well recognized and the mechanisms of reactions with organic substrates have been under investigation by numerous investigators [1–4]. In 1968 Fauvarque and in 1969 Blomberg and Mosher [5,6], presented evidence supporting a SET pathway in the reaction of Grignard reagents with ketones. A few years later Holm [7] proposed a mechanism similar to that proposed by Fauvarque and Blomberg–Mosher and presented strong supporting arguments based on linear free energy studies. His conclusions were broader than previous workers stating that t-butyl Grignard reagents react with aromatic ketones via a SET process and methyl Grignard reagents react via a polar process. More recently, Okubo has presented convincing evidence for the intermediacy of ketyl radicals in the reactions of Grignard reagents with ketones [8–10].

Our research group has focussed on the mechanism of Grignard Compound addition to ketones for two decades [1]. Prior to 1972, we had established that both

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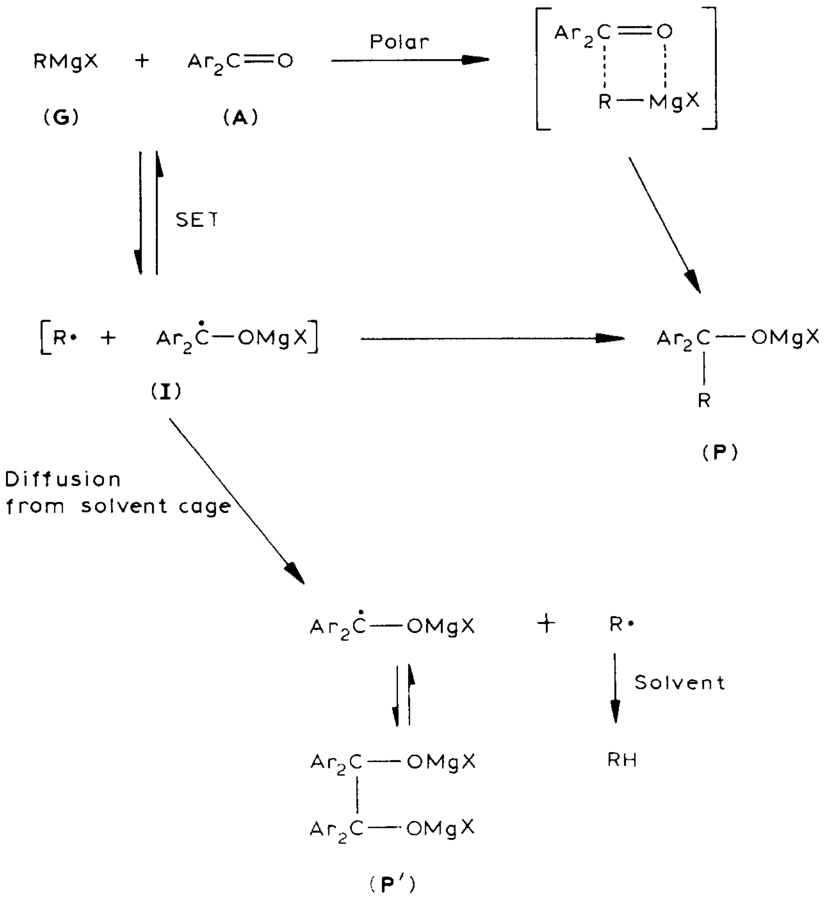
RMgX and R_2Mg species exist in solution and thus both species are capable of reacting with carbonyl compounds. We also established that mechanistic studies involving Grignard reagent addition to organic substrates should be carried out using Grignard reagents (particulary the bromides) at low concentration in order to avoid the existence of higher associated species in solution which when not avoided in the past resulted in unresolvable kinetic analysis. More recently we have been able to show by means of cyclizable free radical probes that indeed free radicals are involved in the reaction of 1°, 2° and 3° Grignard reagents with aromatic ketones [2,3]. Today, based on the work of others and own studies [2,3,12,13], we suggest that the reaction of Grignard reagents (1°, 2°, and 3°) with aromatic ketones is best represented as proceeding via a single electron transfer (SET) pathway at least to some extent depending on the nature of the Grignard reagent, the ketone, and the solvent (Scheme 1).



Sometime ago we reported a kinetic study of the reaction of Grignard reagents with aromatic ketones by following the disappearance of the UV absorption band formed as a result of the complex between the Grignard reagent and the ketone [13]. However, no one has reported using epr techniques to establish the single electron transfer nature of Grignard reactions by observing the rate of disappearance of the paramagnetic intermediate and relating it to the appearance of product. In view of the fact that this technique would provide a much simpler method for determining SET in a particular reaction than has been used heretofore, we would now like to report studies which indicate that the rate constant of the Grignard reaction can be obtained by following the rate of disappearance of the paramagnetic intermediate and this rate constant related to the rate constant obtained for the appearance of product. Because of the complicated nature of the Grignard reagent-substrate mixture, the most useful and reliable method to obtain kinetic results has been to employ pseudo-first order conditions with the Grignard reagent present in excess [4]. In this situation, the concentration of Grignard reagent is virtually unchanged during the reaction. If the concentration of the paramagnetic intermediate is found to decrease during the same time period that the product is being formed, then an electron transfer process is at least consistent with the data.

Results and discussion

Reaction of methylmagnesium bromide with 2-methylbenzophenone

For many years, the reaction of methyl Grignard reagents with ketones was not easily interpreted in terms of the nature of alkyl transfer in that many reactions showed some of the characteristics of both polar and SET pathways [12]. Recently, we have reported that not only tertiary Grignard reagents, but also primary Grignard reagents react with aromatic ketones in both diethyl ether and THF by an ET process [3], although aliphatic ketones appear to react by a polar process. Such a result is reasonable when one considers that aromatic ketones are much more easily reduced than aliphatic ketones. Although the detection of an SET pathway has been a somewhat difficult task, and detection of free radicals does not necessarily mean that the reaction is proceeding by an SET pathway, we now report that detection and reaction rate determinations of radical reactions by ESR spectroscopy provide evidence for SET pathways in organometallic reactions.

When a 10 fold excess of methyl magnesium bromide (**1**), was allowed to react with 2-methylbenzophenone (**2**) in ether at room temperature, a light pink color developed rapidly and the solution was found to be EPR active. The intensity of the EPR signal increased rapidly to a maximum (ca. 0.01% relative to the initial concentration of ketone [14]) then decreased slowly in a first order fashion (Table 1,

TABLE 1

EPR-STUDY FOR THE REACTION OF CH_3MgBr WITH 2-METHYLBENZOPHENONE IN ETHER AT ROOM TEMPERATURE [a,b]

Entry	Time (min)	EPR-Intensity (mm)	ln EPR-Intensity
1	2.5	174	5.169
2	4.0	147	4.990
3	5.5	122	4.804
4	7.0	95	4.554
5	8.5	69	4.234
6	10.0	52	3.951

[a] The initial concentrations were 0.066 *M* for the ketone and 0.066 *M* for the Grignard reagent. [b] The maximum concentration of radical intermediate was ca. 0.01/%.

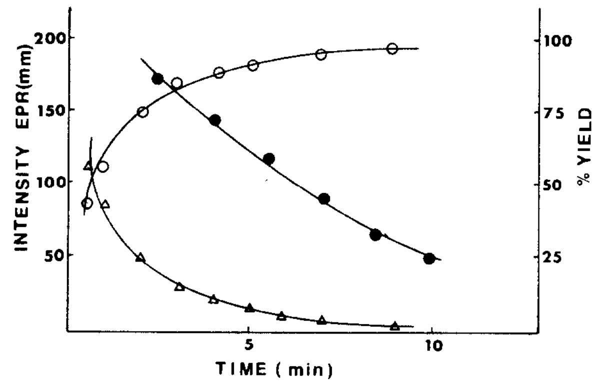


Fig. 1. Reaction of 2-methylbenzophenone with a 10 fold excess of CH_3MgBr in ether at room temperature: (●) intensity of the EPR signal (mm) vs. time (min) (△) recovered ketone(%) vs. time; (○) products(%) vs. time.

Fig. 1). A reaction profile study, as a function of time, has been also carried out indicating the rate of formation of the product and disappearance of the ketone (Table 2). It is shown that the rate of disappearance of ketone (formation of the product) exhibits pseudo-first order behavior (Fig. 1). Expectedly, the concentration of the product is increasing as a function of time, whereas, the concentration of the paramagnetic intermediate is decreasing during the same time period. However, the Grignard reaction can be simply described as in eq. 1 in which G is in excess. Based on the reaction profile study, the rate expression of the reaction would be as shown

$$\mathbf{A} + \mathbf{G} \overset{K}{\rightleftharpoons} \mathbf{I} \overset{k}{\rightarrow} \mathbf{P} \tag{1}$$

A = Ketone K = equilibrium constant **P** = product
G = Grignard reagent **I** = paramagnetic intermediate

$$\frac{-\mathrm{d}[\mathbf{A}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathbf{P}]}{\mathrm{d}t} = k_{\text{profile}}\{[\mathbf{P}_\infty] - [\mathbf{P}]\} \tag{2}$$

TABLE 2

REACTION PROFILE STUDY OF THE REACTION OF CH_3MgBr WITH 2-METHYLBENZOPHENONE IN ETHER AT ROOM TEMPERATURE [a,b,c]

Entry	Time (min)	Carbinol (%)	Ketone	$\ln(P_\infty - P_t)$
1	0.5	44	57	4.043
2	1	56	44	3.784
3	2	74	26	3.258
4	3	85	15	2.708
5	4	89	11	2.398
6	5	92	8	2.079
7	7	96	4	1.386
8	9	98	2	0.693

[a] The initial concentration was 0.066 *M* for the ketone and 0.66 *M* for Grignard reagent. [b] The percent rates were determined by GLC using 9-fluorenone as the internal standard. [c] Yields were normalized.

Assume that: $[\mathbf{A}]+[\mathbf{I}]+[\mathbf{P}]=[\mathbf{A}_0]=[\mathbf{P}_\infty]$ then:

$$\frac{-\mathrm{d}[\mathrm{A}]}{\mathrm{d}t}=\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t}=k_{\text{profile}}\{[\mathrm{A}]+[\mathrm{I}]\} \tag{3}$$

$$\frac{-\mathrm{d}[\mathrm{A}]}{\mathrm{d}t}=\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t}=k_{\text{profile}}[\mathrm{A}] \tag{4}$$

in eq. 2. Since the concentration of the radical intermediate **I** is very small (i.e. $[\mathbf{I}] \approx 0$), eq. 3 can then be simplified to eq. 4. On the other hand, based on the EPR study, the rate expression of the reaction is shown in eq. 5–10.

$$\frac{-\mathrm{d}[\mathrm{I}]}{\mathrm{d}t}=k_{\mathrm{EPR}}[\mathrm{I}] \tag{5}$$

$$K=\frac{[\mathrm{I}]}{[\mathrm{A}][\mathrm{G}]} \tag{6}$$

$$[\mathrm{I}]=K[\mathrm{A}][\mathrm{G}] \tag{7}$$

In the pseudo-first order reaction, [G] is a constant. Therefore:

$$\frac{-\mathrm{d}[\mathrm{I}]}{\mathrm{d}t}=K[\mathrm{G}]\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} \tag{8}$$

$$-\mathrm{K}[\mathrm{G}]\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t}=k_{\mathrm{EPR}}\mathrm{K}[\mathrm{G}][\mathrm{A}] \tag{9}$$

$$\frac{-\mathrm{d}[\mathrm{A}]}{\mathrm{d}t}=k_{\mathrm{EPR}}[\mathrm{A}]=\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} \tag{10}$$

Therefore, comparing eq. 4 with 10, the rate constants in both methods should be consistent with each other (i.e. $k_{\text{profile}} \approx k_{\mathrm{EPR}}$). The pseudo-first order rate constant for the radical intermediate decay process observed by EPR spectroscopy (Table 1) has been calculated to be $k_{\mathrm{EPR}} = 2.7 \times 10^{-3}$ s^{-1} (correlation coeff. = −0.9932). The pseudo-first order rate constant of this reaction observed from the reaction profile by following the formation of the product $(\mathbf{P}_\infty - \mathbf{P}_t)$ is $k_{\text{profile}} = 6.5 \times 10^{-3}$ s^{-1} (correlation coeff. = −0.9941). These two rate constants do not match perfectly possibly because the equilibrium between the reactants and paramagnetic intermediate is being reached late. Therefore, the observed rate constant obtained by EPR spectroscopy (k_{EPR}) is smaller. In fact, the two rate constants (k_{EPR} and k_{profile}) are closer when the data are taken after the equilibrium has been reached (i.e. the latter stage of the reaction 2.7 and 5.6×10^{-3} s^{-1}). It is, of course,also possible that the difference between these two observed rate constants may be due to a competition between the ET and polar processes being involved in the reaction pathway. Nevertheless, these kinetic data and the observation that the rate of disappearance of the paramagnetic intermediate is related to the rate of appearance of product supports the suggestion that the reaction of methylmagnesium bromide with benzophenone proceeds via a single electron transfer pathway.

Reaction of phenylmagnesium bromide with 2-methylbenzophenone

Since the reactions of substituted benzophenone with phenylmagnesium bromide have been well established as proceeding via an ET pathway [8–10], this reaction should be a good model system to examine the relationship between k_{EPR} and

TABLE 3

EPR-STUDY FOR THE REACTION OF C_6H_5MgBr WITH 2-METHYLBENZOPHENONE IN ETHER AT ROOM TEMPERATURE [a,b]

Entry	Time (min)	EPR-Intensity (mm)	ln EPR-Intensity
1	2.5	194	5.268
2	4.0	138	4.927
3	5.5	100	4.605
4	7.0	75	4.317
5	8.5	59	4.077
6	10.0	49	3.892

[a] The initial concentrations were 0.066 *M* for the ketone and 0.66 *M* for Grignard reagent. [b] The maximum concentration of radical intermediate was ca. 0.01% [14].

k_{profile}. When an excess (10 fold) of phenylmagnesium bromide (**3**) was allowed to react with 2-methylbenzophenone in ether at room temperature, a purple color developed rapidly and the solution was found to be EPR active. As in the case of the methyl-Grignard reagent, the intensity of the EPR signal increased rapidly to a maximum (ca. 0.01% relative to the initial concentration of ketone [14]) then decreased slowly in a first order fashion (Table 3, Fig. 2) with $k_{\text{EPR}} = 3.1 \times 10^{-3}\ s^{-1}$ (correlation coeff. = −0.9945). The data for the reaction profile as a function of time are given in Table 4. The profile of the disappearance of the ketone (formation of products in which we assume that both carbinol and pinacol come from the same intermediate) was consistent with pseudo-first order behavior with $k_{\text{profile}} = 5.1 \times 10^{-3}\ s^{-1}$ (correlation coeff. = −0.9920). These two rate constants (k_{EPR} and k_{profile}) are comparable. As mentioned previously, the two rate constants match better when the data are taken from the latter stage of the reaction where the equilibrium between reactants and paramagnetic intermediate has been reached. As expected, the rate constant of the reaction taken from the latter stage (entries 3–8, Table 4) during the time period where the EPR study is performed is $k'_{\text{profile}} = 3.6 \times 10^{-3}\ s^{-1}$ (correlation coeff. = −0.9944). Indeed, these two rate constants (k'_{profile} and k_{EPR}) are the same within experimental error ($3.6 \times 10^{-3}\ s^{-1}$ vs. $3.1 \times 10^{-3}\ s^{-1}$). Once again, the data provide supporting evidence for the description of the reaction of

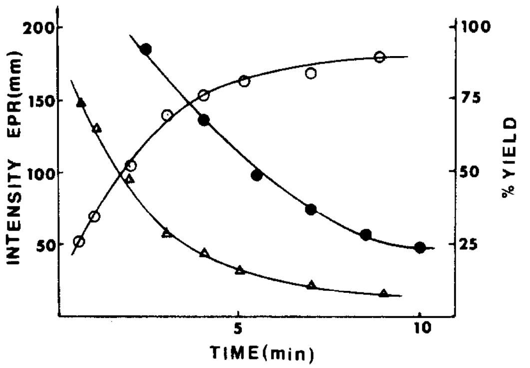


Fig. 2. Reaction of 2-methylbenzophenone with a 10 fold excess of C_6H_5MgBr in ether at room temperature: (●) intensity of the EPR signal (mm) vs. time, (min); (△) recovered ketone(%) vs. time; (○) product (%) vs. time.

TABLE 4

REACTION PROFILE STUDY OF THE REACTION OF C_6H_5MgBr WITH 2-METHYLBENZOPHENONE IN ETHER AT ROOM TEMPERATURE [a,b,c]

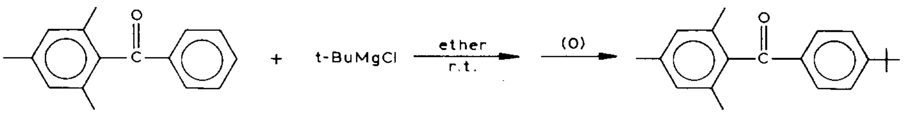
Entry	Time (min)	Product(%) [d]	Ketone (%)	ln ($P_\infty - P_t$)
1	0.5	26	74	4.304
2	1	34	66	4.190
3	2	53	47	3.850
4	3	71	29	3.367
5	4	77	23	3.135
6	5	83	17	2.833
7	7	89	11	2.398
8	9	92	8	2.079

[a] The initial concentrations were 0.066 *M* for the ketone and 0.66 *M* for Grignard reagent. [b] The percent yield were determined by NMR using 2-t-butylanthraquinone as standard. [c] Yields were normalized. [d] Carbinol and pinacol.

phenylmagnesium bromide with benzophenone as an SET process and the rate of disappearance of the paramagnetic intermediate is realted to the rate of appearance of products (disappearance of the ketone) (Fig. 2).

Reaction of t-butylmagnesium chloride (4) with substituted benzophenones

Reaction of t-butylmagnesium chloride (**4**) with benzophenone has been well studied in the past. It is known that the reaction proceeds mainly via a SET pathway [3]. When 2,4,6-trimethylbenzophenone (**5**) was allowed to react with a 10 fold excess of **4** in ether at room temperature, a purple color developed rapidly and the solution was found to be EPR active. However, we also found that this was a very fast reaction and 99% of the reaction was over within 30 s to yield 2,4,6-trimethyl-4'-t-butylbenzophenone (eq. 11). When a more sterically hindered ketone, 2,2'4,6,6'-pentamethylbenzophenone (**6**), was allowed to react with a 10 fold excess of **4**, a deep purple color developed rapidly and the solution was found to be EPR active. Unfortunately there was no decrease in absorption observed during the ensuing 20 h period, however, 1,6-addition product was formed during this time period. It is possible that a paramagnetic intermediate as a radical pair which is formed inside the solvent cage to produce product. However, since the t-butyl radical is stable, the free ketyl radical has more time to diffuse out of the solvent cage (Scheme 1) and mask the EPR evaluation of the rest of the reaction. Therefore, it was not possible to determine the rate constant for reaction of the t-butyl-Grignard reagent with an aromatic ketone.



(11)

Conclusion

The reaction of methyl-, phenyl-, and t-butyl-Grignard reagents with substituted benzophenones was examined in order to compare the rate constant for the formation of the product (disappearance of the ketone) with the rate constant obtained for the disappearance of the paramagnetic intermediate by EPR spectroscopy. In order to simplify the study, pseudo-first order conditions with respect to the Grignard reagent were employed. We found that the concentration of the paramagnetic intermediate generated in the reaction was shown to decrease in a first order fashion with a pseudo-first order rate constant (k_{EPR}) which is consistent with the pseduo-first order rate constant (k_{profile}) describing the rate of disappearance of the ketone (appearance of product) in the cases of methyl- and phenyl-Grignard reagents. However, with t-butyl-Grignard reagent, the reaction proceeded either too fast (in the case of **5**) or too slow (in the case of **6**, due to the steric hindrance in the ketone) and the disappearance of the paramagnetic intermediate was masked by the higher concentration of escaped ketyl. Nevertheless, considering the available data, it seems that the rate constant for the reaction of Grignard reagents with aromatic ketones can be obtained by following the rate of disappearance of the paramagnetic intermediate or the rate of appearance of product (disappearance of ketone). The fact that the paramagnetic intermediate, in the case of the methyl- and phenyl-Grignard reagents, decreases during the same time period that the product is appearing is further evidence that the two events are related. All the results reported in this study strongly support our previous suggestion that the reaction of Grignard reagents with aromatic ketones proceeds via a single electron transfer pathway.

Experimental

General procedures and materials. Reagent grade anhydrous diethyl ether (Fisher) was distilled under nitrogen from a deep purple solution of sodium benzophenone ketyl. Samples of t-butyl chloride (b.p. 51°C, CaH_2), bromobenzene (b.p. 156°C, CaH_2), 2-methylbenzophenone (125–126°C at 0.3 mmHg) were purchased from Aldrich and purified by distillation. Reagent grade 2,6-dimethylbenzoic acid (Aldrich), $AlCl_3$ (Fisher), methyl bromide (Matheson) and mesitylene (Aldrich) were used as received. Samples of thionyl chloride (b.p. 76°C, $(PhO)_3P$) and carbon disulfide (b.p. 46°C, P_2O_5) were purchased from Fisher and purified by distillation. Resublimed magnesium (chips 99.95%) was purchased from Alfa.

Gas chromatographic analyses were conducted on a Varian 3700 (FID) instrument coupled to a Varian CDS III electronic integrator using a DB-1 capillary column. Quantitative GLC analyses were obtained with the use of response factors, corrected peak areas and using internal standards. Proton NMR spectra were recorded on a Brucker Ft 300 spectrometer using TMS as a standard.

Preparation of 2,4,6-trimethylbenzophenone (5). Following the literature procedure [15], **5** was obtained in 90% yield, b.p. 128°C/0.4 mmHg.

Preparation of 2,2′,4,6,6′-pentamethylbenzophenone (6). Following the literature procedure [16], **6** was obtained in 19% yield, m.p. 85–86°C.

Preparation of Grignard reagents. Grignard reagent solutions were prepared as previously described [13]. The clear Grignard reagent solutions were standardized by standard magnesium analysis (EDTA titration), total base analysis, and halide analysis prior to use.

General procedure for kinetics experiments. Desired amounts of Grignard reagents and a solution of the ketone were combined under nitrogen in an EPR tube. The decrease of the EPR signal was monitored by repetitious scans from the time immediately after mixing the reagents. The concentration of radical species was estimated by a comparison of the peak height of the first derivative EPR signal generated in the reaction with the peak height of the signal obtained from a sandard solution of 2,2,5,5-tetramethylpyrrolidine-3-carboxamide-1-oxyl radical [14].

For the EPR study of the reaction of CH_3MgBr (**1**) with 2-methylbenzophenone (**2**): 1 ml of a 1.32 *M* solution of **1** in ether was placed in a side bulb of an EPR tube containing 1 ml of a 0.132 *M* solution of **2** in ether in the bottom of the same tube. Immediately after mixing these reactants, the measurements of the EPR signal intensities were made at appropriate time intervals.

A reaction profile study with respect to time for the same reaction was performed by carrying out several sets of experiments and quenching each set at an appropriate time: To 1 ml of a 0.132 *M* solution of **2** in ether under N_2 was added 1 ml of a 1.32 *M* solution of **3** in ether at room temperature. After a certain time period, with stirring, the reaction mixture was quench with ammonia water and the resulting solution extracted with ether. The ether extracts were dried over $MgSO_4$ and after filtration, the solvent was removed at reduced pressure. The residue was then analyzed by proton NMR.

*Reaction of 2,4,6-trimethylbenzophenone (**5**) with t-butylmagnesium chloride (**4**)* To 0.7 ml of a 0.073 *M* solution of **5** in ether under N_2 was added 1 ml of a 0.496 *M* solution of **4** in ether at room temperature. After a certain time period, with stirring, the reaction mixture was quenched with ice water. The solution was then treated with 30% of hydrogen peroxide and extracted with ether. The extracts were dried over $MgSO_4$ and, after filtration, the solvent was removed at reduced pressure. The residue was then analyzed by proton NMR.

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