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Ketyl Radicals Formed in Grignard Reaction. IV.[1] Sterically Hindered Ketyl Radicals in Nuclear Replacement and Conjugate Addition

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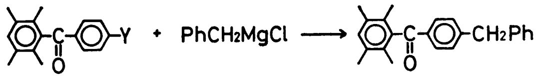
The reaction in which 4′-methoxy and 4′-cyano substituents on 2,3,5,6-tetramethylbenzophenone are effectively replaced by benzyl- and *t*-butylmagnesium chloride was examined by means of ESR measurements. Both the original and the "replaced" ketyl radicals were identified, and an electron-transfer mechanism similar to that of S_{RN}-type reactions was proposed. Some sterically hindered $\alpha\beta$-enones were also found to form detectable amounts of ketyl radicals. The factors governing the production ratio of the normal and the conjugate adduct were discussed.

Several reports have been given on evidence for the electron-transfer(ET) mechanism of Grignard reaction.[2,3] The course of the reaction of PhMgBr with benzophenone is affected greatly by the steric hindrance of *ortho*-methyl groups; the group on the former reagent tends to form benzopinacol whereas the same group on the latter to form the nuclear phenylated product.[1] The formation of these "abnormal" products can be explained by the ET-mechanism *via* ketyl radicals. Not only the mode of appearance but also the spin-distribution on the radicals have turned out to be dependent upon the magnitude of the steric effect. Thus, similar steric effects are expected to be operative in the Grignard reactions of the several different types of ketones. This paper gives the results of the ESR studies on the two "abnormal" Grignard reactions: 1) the nuclear replacement of anionoid substituents on hindered benzophenones, and 2) the conjugate addition to the *ortho*-methyl derivatives of chalcone, 2-benzoylbenzofuran, and 3-benzylidenecamphor.

Results and Discussion

Nuclear Replacement of Hindered Benzophenones. Recently the ET-mechanism for the nuclear *ortho*-phenylation of benzoylmesitylene in the reaction with PhMgBr was proposed.[4] Benzophenone itself undergoes unclear *t*-butylation, which has been explained also by the ET-mechanism.[5] Fuson and his co-workers pointed out that some anionoid substituents (methoxyl, cyano, and acetoxyl) were effectively available for the analogous nuclear alkylation or arylation.[6] As the first step in the present work, the "replacement" reaction of the 4′-MeO and 4′-CN substituents of 2,3,5,6-tetramethylbenzophenone (benzoyldurene) with $PhCH_2MgCl$ (Scheme 1) was examined by ESR technique.



(1) (2)

Y : OMe and CN

Scheme 1.

For the sake of simple analysis of ESR spectra, the 2,3,5,6-tetramethylphenyl(duryl) group is advantageous since it gives no resolvable splitting[7] as a result of the inhibition of spin-delocalization due to the twisting of the group out of the plane of the carbonyl group.[8] Though all the spectra were not fully-resolved, they can be analyzed by considering only the hydrogen atoms of the unhindered aryl groups. The structure and the coupling constants of the radicals identified are summarized in Table 1.

When the two 4′-substituted benzoyldurenes(**1**) were treated with five equivalents of $PhCH_2MgCl$ in tetrahydrofuran(THF) in a vacuum and at room temperature, the colorless (Y=OMe) or pale yellow (Y=CN) solution turned first pink and then reddish brown rapidly. Replacement product(**2**) was obtained after 1 h in a good yield. The highest radical concentrations, observed after 30 min after mixing, were estimated to be *ca.* 6 mol% based on the concentration of the original ketones. The ESR spectrum (Fig. 1a) obtained after the reaction solution had turned reddish brown, was independent of the 4′-substituents. When $PhCD_2MgCl$ is used, the spectrum changes to the one which has weak narrow quintets (Fig. 1b). The spectrum is thus ascribed to a ketyl radical (Rp)· which has been "replaced" by the benzyl group. The large coupling constant of the benzylic hydrogen, a_{α}^{H} (Table 1), seems to reflect the fact that the $Q_{C\text{-}CH_3}^{H}$ value (27.2) is larger than the $Q_{C\text{-}H}^{H}$ value (23.7).[9]

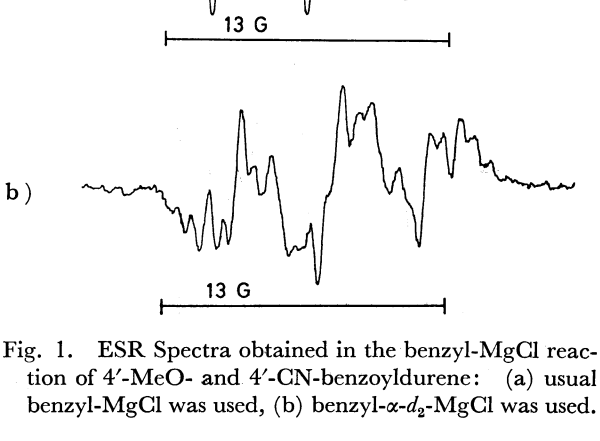
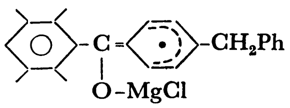
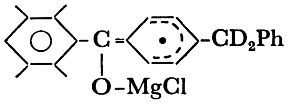
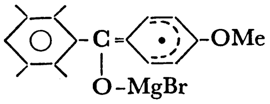
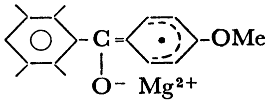
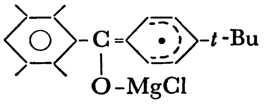
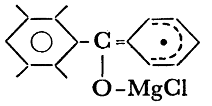
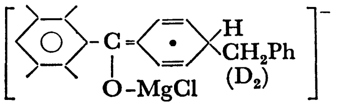


Fig. 1. ESR Spectra obtained in the benzyl-MgCl reaction of 4′-MeO- and 4′-CN-benzoyldurene: (a) usual benzyl-MgCl was used, (b) benzyl-α-d_2-MgCl was used.

Table 1. Coupling constants of Grignard ketyls of some benzoyldurenes

No.	Structure of ketyls	Coupling constants (G) a_p^H	a_o^H	a_m^H	a_α^H	Spectrum corresponding to Fig.
1		—	4.44	1.39	4.0	Fig. 1a
2		—	4.44	1.39	$a_\alpha^D=0.62$	Fig. 1b
3		—	4.44	1.52	—	Fig. 2
4		—	4.44	1.52	—	(Fig. 2)
5		—	4.44	1.46	—	Fig. 3
6		5.69	4.38	1.32	—	Fig. 4
7		2.91	5.83	1.39	—	Fig. 4

When PhMgBr was used instead of $PhCH_2MgCl$, the solution turned pink, the coloration becoming deep purple. The radical concentration increased gradually and reached *ca.* 30 mol% of the original ketone after 5 h. A partially resolved spectrum (Fig. 2) was obtained. It was identical with that of the Mg-ketyl prepared by use of Mg-amalgam. However, only the original ketone was recovered when the deeply colored solution was hydrolyzed after 1 h. Thus, the pink coloration observed transiently in the initial stage of the $PhCH_2MgCl$ reaction can be ascribed to the ketyl radical of **1**.

t-Butylmagnesium chloride reacts similarly with **1** (Y=OMe) giving *para-t*-butylated ketone in a high yield.[10] A color change similar to that of $PhCH_2Mg$-Cl reaction was observed though the radical concentration was low (*ca.* 2 mol%). This low radical concentration is recognizable as a result of the higher reactivity of *t*-butyl reagent than that of benzyl reagent.[2] The obtained ESR spectrum is shown in Fig. 3. Since the spectrum differs from that of the original ketyl of **1**, it can be ascribed to that of the "replaced" ketyl radical (Table 1). The difference between the values of a_m^H of No. 1, 3, and 5 is understood as that between the magnitudes of electron-repelling ability of the respective substituents.

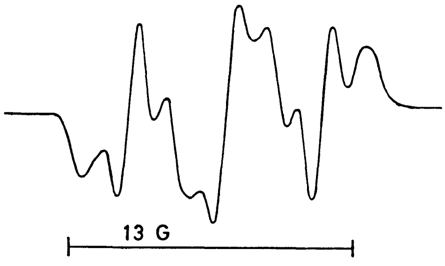


Fig. 2. ESR Spectrum obtained in the phenyl-MgBr and/or Mg-amalgam treatment of 4′-MeO-benzoyldurene.

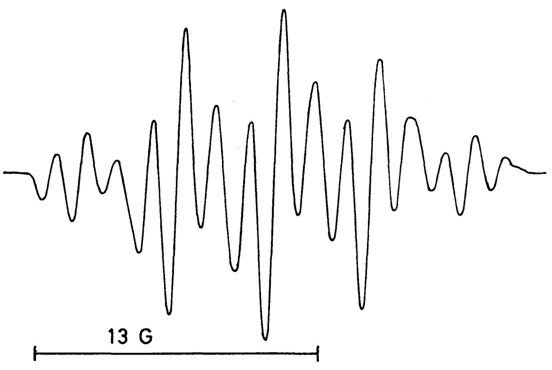
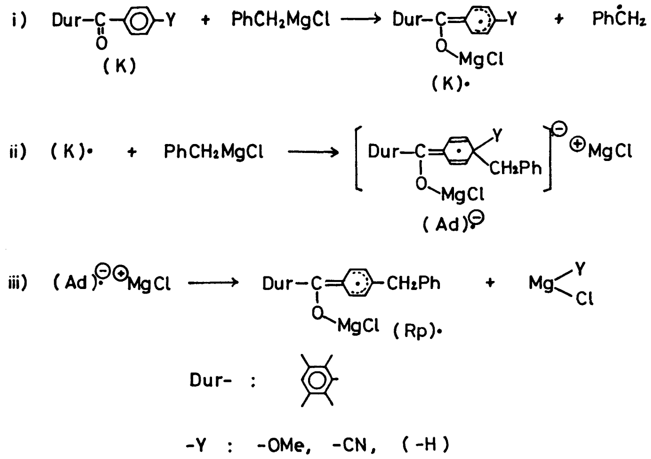


Fig. 3. ESR Spectrum obtained in the *t*-butyl-MgCl reaction of 4′-MeO-benzoyldurene.

Since both the original and the "replaced" ketyl radicals were identified and the low radical concentration in the $PhCH_2MgCl$ and/or *t*-BuMgCl reaction is attributable to the high reactivity of these reagents, the replacement reaction can be explained by the ET-mechanism shown in Scheme 2.

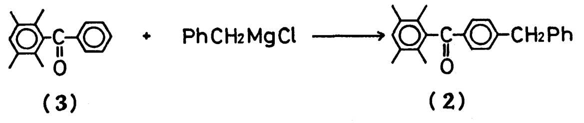
The benzyl radical produced in step i) is in the coordi-



Scheme 2.

nating state to the Mg atom, and would be less reactive than the ordinarily generated "free" radicals; the radical does not necessarily react with the ketyl radical (K)· in the recombination manner. In fact, most part of the benzyl radical escapes out of the solvent cage and abstracts hydrogen from the THF molecule.11) Since neither benzyl methyl ether nor benzyl cyanide was detected, the substituent Y would be eliminated as anoin Y$^-$ and the process can be formulated by the sequence of steps ii) and iii). The formation of the adduct radical anion species (Ad)$^{\overline{\cdot}}$ $^+$MgCl is possible since the O–Mg linkage in (K)· is covalent due to the largest electronegativity of Mg among the alkali and alkaline-earth elements; (K)· should thus be neutral. The formation of such an aggregated state4) is compatible with the observation of the highly aggregated Grignard species in the presence of oxygen-containing compounds.12)

The postulate on the formation of (Ad)$^{\overline{\cdot}}$ $^+$MgCl is rationalized by the following study on the nuclear substitution reaction of benzoyldurene itself (**3**) with PhCH$_2$MgCl (Scheme 3).13) The *para*-benzylated product (**2**) was isolated (yield 23%) after the reaction solution had been left to stand at room temperature for 4 h. The ESR spectrum consists of thirteen lines (Fig. 4) and is not influenced by the use of PhCD$_2$MgCl, in contrast with the case of **1**. The original ketyl of **3** has thirteen lines with the relative strength of 1 : 2 : 1 : 2 : 5 : 4 : 2 : 4 : 5 : 2 : 1 : 2 : 1, whereas the adduct radical anion (Scheme 2; (Ad)$^{\overline{\cdot}}$, Y=H) shows also thirteen lines but with different relative strength of 1 : 2 : 2 : 2 : 3 : 4 : 4 : 4 : 3 : 2 : 2 : 2 : 1 (*cf.* Table 1, No. 6 and 7). The spectrun (Fig. 4) with the apparent relative strength of 1 : 1.9 : 1.2 : 1.0 : 2.4 : 2.6 : 1.6 : 2.6 : 2.4 : 1.0 : 1.2 : 1.9 : 1 was reconstructed by superposing the stronger signals of the original ketyl (No. 6) on the weaker ones of the adduct radical anion (No. 7). The (AdH)$^{\overline{\cdot}}$ species does not undergo the hydrogen-transfer (Scheme 4a)4) as easily as the (Ad)$^{\overline{\cdot}}$ species undergoes the Y$^-$-transfer. Thus, the (AdH)$^{\overline{\cdot}}$ becomes detectable, but not the "replaced" radical (Rp)·. The formation of **2** would be caused by the air-oxidation of AdH during the course of isolation (Scheme 4b).5)



Scheme 3.

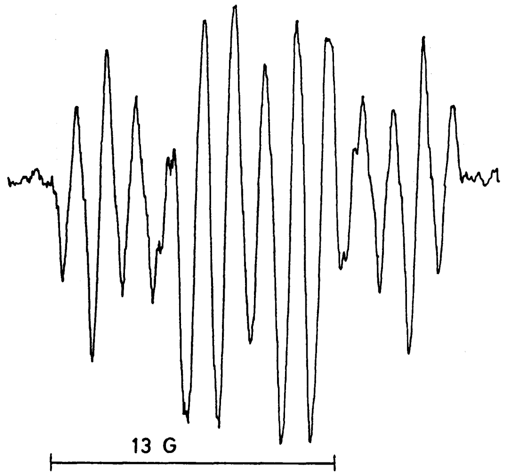
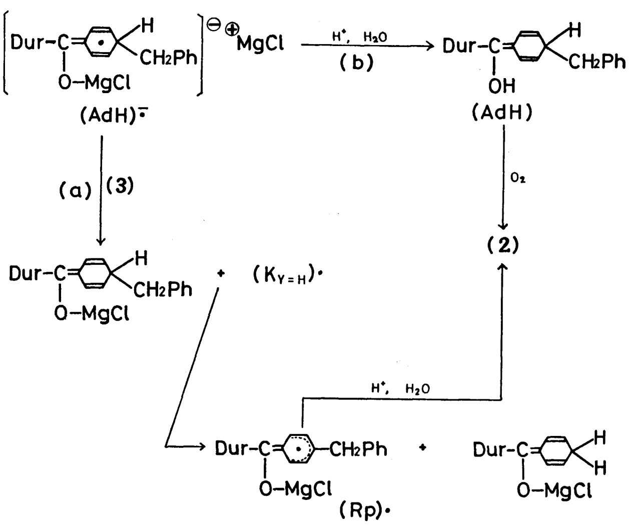


Fig. 4. ESR Spectrum obtained in the benzyl-MgCl and/or benzyl-α-d_2-MgCl reaction of benzoyldurene.



Scheme 4.

If we compare the reaction profiles of **1** with those of **3**, the former reaction is characterized in terms of "replacement", the latter in terms of "addition." The definitive ease of the former reaction is consistent not only with the high spin-density on the unhindered aryl groups,8) but also with the formation of (Ad)$^{\overline{\cdot}}$ favoring the elimination of Y$^-$. Such an intermediacy of the radical anion species resembles what was postulated in a number of S_{RN}-type reactions.14) The electrolytically reductive elimination,15,16) as well as the Grignard replacement,17) of the anionoid substituents from benzonitrile derivatives have also been reported.

In order to estimate the effect of 4′-anionoid substituents on the ET-process, the initial concentrations of ketyl radicals produced on the PhMgBr treatment of 4′-F-, 4′-Cl- and 4′-MeO-benzoylmesitylenes were

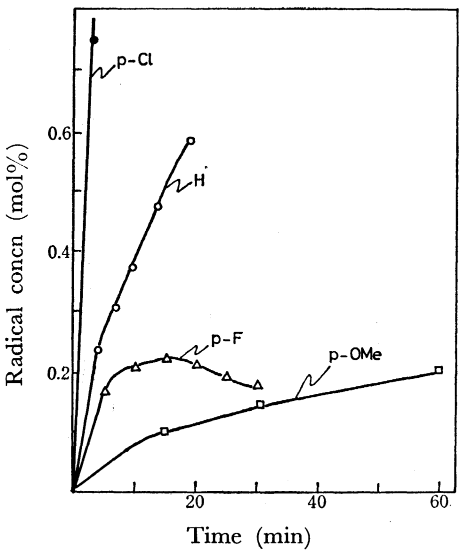
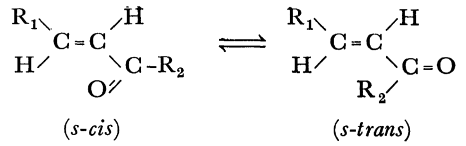


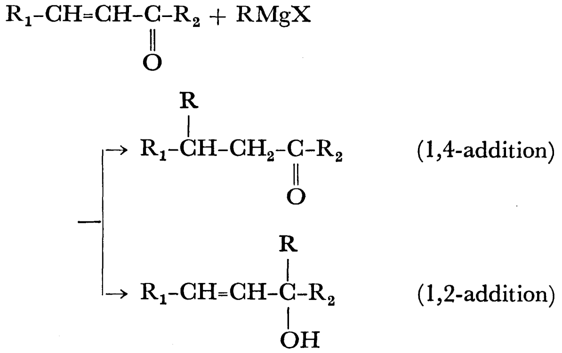
Fig. 5. Radical concentrations at the initial stage of the phenyl-MgBr treatment of benzoylmesitylenes.

compared. Despite the high radical concentrations, no replacement product was obtained after this treatment for 1 h. The radical concentrations, measured by the over-modulation technique, were tentatively corrected on the basis of the relative total width of the well-resolved spectra, respectively (see Experimental). As shown in Fig. 5, the chloro derivative accelerates and the methoxy derivative retards the ET-velocity, whereas the fluoro derivative greatly reduces the radical concentration. However, the estimation by means of visible spectral absorbance verified the high ET-velocity of the fluoro derivative comparable to that of the chloro derivative. The seemingly low radical concentration, as well as the noticeably reduced fluidity of the deeply colored solution, suggests the presence of aggregated diamagnetic dimers which might be formed by the coordination of unhindered fluorine atoms to Mg atom. Probably such an additional coordination through the lone-pair electrons of substituents, when it is located on a position appropriate for the reactivity of the Grignard reagent used, favors the replacement reaction. In fact, the introduction of anionoid substituents such as methoxyl group[18] or bromine atom[19] on the *ortho*-position of benzophenones is effective for the nuclear *ortho*-phenylation in the "replacement" manner.

Considering the difference between the markedly slow *ortho*-phenylation of benzoylmesitylene[4] and the rather rapid *para*-benzylation of benzoyldurene,[13] the C_{phenyl}–Mg linkage is stronger than the C_{benzyl}–Mg linkage.

Conjugate Addition to αβ-Enones. The earliest systematic work by Kohler[20] on the mode of the Grignard addition to open-chain αβ-enones (Scheme 5) reveals the steric effect of R_1, R_2, and R. If R_2 is H(aldehydes), only the normal 1,2-addition takes place. As R_2 becomes bulkier, the conjugate 1,4-addition becomes predominant. This is understandable since the bulky R_2 favors the *s-cis* conformation which is appropriate for the six-membered cyclic structure of transition state. When R_1 is phenyl and R_2 is ethyl, some alkylmagnesium bromides and benzylmagnesium chloride gave 68—70% yields of the conjugate adducts whereas phenylmagnesium bromide gave only the 40% yield.[20] This reveals the strength of C_{phenyl}–Mg linkage, which may be loosened only slightly in the transition state, making it suitable for normal addition.

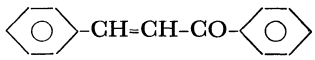
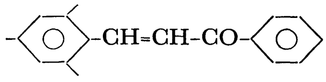
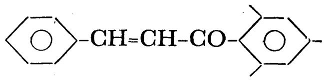
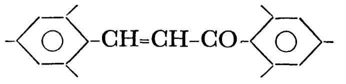




Scheme 5.

Even in the PhMgBr reaction, chalcone(**4**) has been reported to give the conjugate adduct almost exclusively.[20] Though the product resulting from the radical dimerization at the β-carbon has been reported,[21] detection of the Grignard ketyl of **4** could not be made because it should react more rapidly than benzophenone[1] owing to its less-crowded molecular structure resulting from the interposition of the –CH=CH– group. Thus, the present author used the sterically hindered chalcones (Table 2) which have one or two mesityl groups instead of the phenyl groups. Attempts to detect ketyl radicals at room temperature in the PhMgBr reaction were unsuccessful even with the use of these chalcones. The electrolytic reduction method was applied. Though all the radical anions of **5**, **6**, and **7** were short lived and the ESR spectra obtained

Table 2. Beta-hydrogen coupling constants and apparent life-times of chalcones

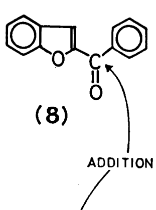
	Chalcones	a^H_β	Order[a)] of life-time
(**4**)		11.3—12.2	3
(**5**)		13.3—13.9	2
(**6**)		—[b)]	(4)
(**7**)		14.1—15.2	1

a) The radical anion which has the apparently longest life-time is indicated by 1. b) The radical anion is very short-lived and a^H_β could not be determined.

were poorly resolved, they consisted of the widely separated two equivalent parts due to the large β-H coupling constants.[22,24] The observed a_β^{H} values accompanied by the order of the apparent life-times are summarized in Table 2.

The a_β^{H} values of **5** and **7** larger than the value of **4** indicate that the spin-delocalization is suppressed by the mesityl substitution. The life-times in cases of **5** and **7** longer than those of **4** and **6** can be explained by the steric hindrance due to the β-mesityl group against the dimerization at the β-carbon.[22] However, all the chalcones **4**—**7** gave the conjugate adducts in the PhMgBr reaction.

In the o-MeC$_6$H$_4$MgBr treatment, **5** solely produced the short-lived Grignard ketyl detectable at room tempetrature; $a_\beta^{\mathrm{H}}=17.7$—$18.9$ G.[25] This is attributable to the following: 1) slower addition process of the o-tolyl reagent than that of the phenyl reagent,[1] 2) lower spin-density on the β-carbon than that of **7**, and 3) the steric hindrance due to the β-mesityl group against addition. The explanation suggests the existence of a correlation between the mode of addition and the spin-distribution. This is supported by the HMO-calculation which shows the high spin-density on the β-carbon comparable to that on the carbonyl-carbon.[24] This is exemplified also by the following examples.



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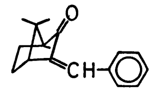

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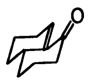

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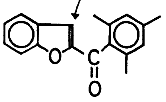

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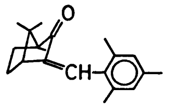

(11)

2-Benzoylbenzofuran(**8**) reacts in the normal mode, and its trimethyl derivative(**9**) in the conjugate mode.[26] The latter displays a pink color of the Grignard ketyl for *ca.* 1 h in the o-MeC$_6$H$_4$MgBr treatment at room temperature; $a_\beta^{\mathrm{H}}=7.8$ G. The fair stability as well as the large a_β^{H} is explained in terms of the nuclear phenylation of benzoylmesitylene.[4]

The bridged cyclic enones, 3-benzylidenecamphor(**10**) and its trimethyl derivative(**11**), gave the conjugate adducts exclusively.[27] On the treatment of **10** and **11** with o-MeC$_6$H$_4$MgBr, the fairly long-lived ketyl radical of the latter camphor was detected at room temperature; $a_\beta^{\mathrm{H}}=4.3$ G. The small coupling constant is explicable by the incomplete co-planarity of the grouping $\mathrm{O{=}\overset{|}{C}{-}\underset{|}{C}{=}CH{-}}$; the mode of addition in this case is governed solely by the rigid *s-cis* conformation.

It can be suggested that 1) the spin-distribution in the ketyl radical, 2) the conformation of $\alpha\beta$-enones, and 3) the strength of C–Mg linkage are the three main factors governing the mode of the Grignard addition to $\alpha\beta$-enones. The result showing that $\Delta^{8,8a}$-1-octalone (**12**) gave only the 43% yield of the conjugate adduct in the PhMgBr reaction[28] is partly attributable to the strong C$_{\mathrm{phenyl}}$–Mg linkage which favors the normal 1,2-addition.

General Discussion. Holm[2] studied the behavior of some alkyl Grignard reagents in the electrolytic oxidation and their thermographically-measured kinetic behavior in the reaction with benzophenone, and discussed the correlation between the two kinds of behavior on the basis of the ET-mechanism. House and Weeks[29] utilized the *cis-trans* isomerization of enone-radical anion, as well as the skeletal rearrangement of radical anion, as means to distinguish the ET-mechanism from the direct nucleophilic attack mechanism in the reaction with methyl-carbanionic reagents. The effect of the strength of C–Mg linkage has not been taken into account. The steric effect would be an additional factor affecting the boundary between the two mechanisms. However, the fact that the steric hindrance of both ketones and Grignard reagents makes it possible to detect the intermediate ketyl radicals by the ordinary ESR technique suggests the possibility of the ET-mechanism of Grignard reaction.

Experimental

Materials. All the benzoyldurenes and benzoylmesitylenes were prepared from durene and mesitylene respectiveley by the Friedel-Crafts reaction with the corresponding benzoyl chlorides.[4,6] Chalcones **4**—**7** were prepared by the aldol condensation of the corresponding benzaldehydes and acetophenones.[20] 2-Benzoylbenzofurans **8** and **9**[26] and 3-benzylidenecamphors **10** and **11**[27] were prepared according to the reported methods. Commercial halogen compounds, including benzyl-α-d_2 chloride, were used for the preparation of Grignard reagents.

Procedures. Grignard reagents in THF were prepared as usual, and stored in sealed bottles under N$_2$ atmosphere. The preparation of samples for ESR measurements were similar to those described previously;[1,8] the molar concentrations of ketones and Grignard reagents were 1.4×10^{-4} and 7.0×10^{-4}, respectively.

Radical concentrations were determined by the over-modulation technique using a reference solution of galvinoxyl in THF.[1] The values obtained by the PhMgBr treatment of benzoylmesitylenes (Fig. 5) were corrected on the basis of the total widths of the resolved spectra: benzoylmesitylene 20.9 G, chloro derivative 16.3 G, fluoro derivative 29.6 G, and methoxy derivative 16.8 G. In order to obtain a well-resolved spectrum, a small portion of the reaction mixture in the measurement cell was diluted by the vaucum distillation of THF from the reaction vessel; the spectra (Figs. 1—4) were not resolvable any further. The visible absorption measurement was also carried out.[1]

For the electrolytic reduction of chalcones **4**—**7**, a similarly shaped simple glass apparatus equipped with two platinum-wire electrodes(the one on the top, anode, and the other at the bottom, cathode, of the cell) was used. Tetrabutylammonium perchlorate(1.0 M) and one of the chalcones (0.2 M) were dissolved in acetonitrile and the apparatus was degassed and sealed off. Since all the radical anions of **4**—**7** were short-lived, the cathode-part of the cell was placed at the center of the ESR cavity. When direct current (0.2 V) was supplied, the green or blue color of radical anions appeared. The apparent life-times(Table 2) were compared based ron the relative time in which the radical anion had been detected by ESR after the direct current was cut off.

Reaction products were separated by means of TLC and/or column chromatography, and identified by their mp and NMR spectra.

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