

the magnetically stirred solution. The reaction mixture was then allowed to warm to room temperature and to stir for 1 h. After addition of 2 mL of water, the organic layer was extracted with ether (2 × 5 mL), and the combined extracts were washed with 2 mL of water and dried (MgSO<sub>4</sub>). Solvent was removed by rotary evaporation, and the residue was dissolved in 2 mL of CH<sub>2</sub>Cl<sub>2</sub> that had been purified by filtration through activated alumina. This solution was added in one portion to a stirred slurry of 0.90 g (4.2 mmol) of pyridinium chlorochromate in 7 mL of purified CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred at room temperature under an atmosphere of nitrogen for 2 h after which 8 mL of ether was added. The organic solution was decanted and the black residue was washed with ether (3 × 4 mL). The combined solutions were washed sequentially with 1 M aqueous NaOH (2 × 20 mL), 2 M HCl (1 × 20 mL), 10% NaHCO<sub>3</sub> (2 × 10 mL), and brine (1 × 10 mL) and then dried (MgSO<sub>4</sub>). Following removal of solvent by rotary evaporation, the crude enone was purified by HPLC (5% EtOAc/petroleum ether, 30–60 °C) to give 10 as a colorless oil in 62% yield. Anal. [2,4-DNP, mp 205.0–6.0 °C (uncorr)]. Calcd for C<sub>20</sub>H<sub>17</sub>N<sub>4</sub>O<sub>4</sub>: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.38; H, 5.22; N, 14.55. <sup>1</sup>H NMR (200 MHz) 7.10–7.40 (m, 5 H), 5.94 (q, *J* = 1 Hz, 1 H), 2.40–2.55 (m, 1 H) 1.95–2.25 (m, 3 H), 1.82 (d, *J* = 1 Hz, 3 H), 1.38 (s, 3 H); <sup>13</sup>C NMR 202.4, 161.2, 142.7, 128.6, 126.7, 126.6, 126.3, 49.0, 35.9, 29.0, 26.6, 23.9; IR (neat) 1680, 1650 cm<sup>-1</sup>; HRMS calcd for C<sub>14</sub>H<sub>17</sub>O 200.1201, found 200.1196.

**5-Deuterio-2-hexanone (15a).** A slurry of 25 g (0.38 mol) of zinc dust and 3 mL of D<sub>2</sub>O was stirred for 10 min at room temperature and filtered by vacuum, and the filter cake was dried at 100 °C (0.2 torr). The zinc was added to a solution of 6.5 g (36 mmol) of 5-bromo-2-hexanone (14a),<sup>15</sup> 8 mL of D<sub>2</sub>O, and 75 mL of anhydrous DME, and the resulting slurry was stirred and heated at reflux for 2 h. After being stirred an additional 20 h at room temperature, the slurry was filtered by vacuum through Celite, the filter cake was washed with pentane (2 × 20 mL), and these washes and an additional 50 mL of pentane were added to the filtrate. The organic solution was washed with water (4 × 100 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was removed by fractional distillation. <sup>1</sup>H NMR 2.34 (t, *J* = 8 Hz, 2 H), 2.05 (s, 3 H) 1.15–1.70 (m, 3 H), 0.90 (m, 3 H); IR (neat) 2160, 1720 cm<sup>-1</sup>; MS, *m/e* 101 (16.8, M<sup>+</sup>), 100 (0.6, M - 1), 43 (100, CH<sub>3</sub>CO<sup>+</sup>); <sup>13</sup>C NMR 208.5, 43.51, 29.7, 26.1, 22.09 (t, *J* = 19.1 Hz), 13.78.

**5-Bromo-5-phenyl-2-pentanone (14b).** A solution of 2.2 g (13.6 mmol) of 5-phenyl-2-pentanone (15c)<sup>18</sup> in 40 mL of CCl<sub>4</sub>

was combined with 3.1 g (17.4 mmol) of freshly recrystallized NBS, and the resulting solution was stirred magnetically and irradiated with a 200-W sunlamp for 30 min. The temperature of the reaction mixture was maintained at 20–25 °C. Following the irradiation, succinimide was removed by vacuum filtration, and the filtrate was washed sequentially with water (20 mL), saturated aqueous Na<sub>2</sub>CO<sub>3</sub>, and water (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and freed of solvent by rotary evaporation. The crude product was reduced directly. <sup>1</sup>H NMR 7.2 (m, 5 H), 4.8 (br t, 1 H), 2.2 (m, 4 H), 1.9 (s, 3 H).

**5-Deuterio-5-phenyl-2-pentanone (15b).** Crude 14b was deuterated in the same manner as was 14a and gave 15b in 68% overall yield from 5-phenyl-2-pentanone (15c). It was purified in the same way as 15a. The level of deuteration was determined by <sup>1</sup>H NMR and mass spectral analyses and was found to vary from less than 40% to 82% monodeuteration at C<sub>5</sub>. Samples containing less than 40% deuterium were not used.

Analysis of the deuterium content of the samples was accomplished by mass spectrometric techniques and application of the following formula to the data: % D = M - (M - 1)[(M + 1)/M]/[M + (M - 1)[1 - (M + 1)/M]] × 100, where M is the molecular ion due to monodeuterated 15b.

**Determination of Kinetic Isotope Effect.** The ketone 15 were separately subjected to the general procedure for preparation of cyclopentenones reported previously,<sup>2</sup> and the products were isolated by GC as before. The reaction was performed at -78 °C with both 15a and 15b and also at room temperature in the case of the latter ketone. Two separate repetitions of each reaction were executed at each temperature.

**Acknowledgment.** The Robert A. Welch Foundation provided partial financial support for this research. Helpful discussions with Prof. Craig Wilcox regarding the determination of the stereospecificity of the insertion reaction are noted with gratitude.

**Registry No.** (R)-(-)-2, 772-14-5; (R)-4, 27798-98-7; 5, 96455-76-4; (R)-5, 96553-63-8; 6, 96455-77-5; (R)-6, 96553-64-9; 7, 51020-13-4; (R)-7, 24432-28-8; 8, 51447-25-7; 10, 96455-78-6; 10 (2,4-DNP deriv.), 119-26-6; 10b, 96553-65-0; 14a, 52355-85-8; 14b, 96455-80-0; 15a, 96455-79-7; 15b, 96455-81-1; 15c, 2235-83-8; D<sub>2</sub>, 7782-39-0.

## Kinetics and Mechanism of the Ivanov Reaction: Reaction of Aldehydes and Ketones with Phenylacetic Acid Magnesium Enediolate<sup>1,2</sup>

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Stopped-flow kinetics of the reaction between aldehydes or ketones and the magnesium enediolate of phenylacetic acid in THF are second order at enediolate concentrations <10<sup>-3</sup> M. At concentrations of 10<sup>-3</sup>–3 × 10<sup>-2</sup> M, the formation of a bis(enediolate) requires a more complex kinetic equation. Second-order rate constants are reported for the reaction of the enediolate with a number of aldehydes and ketones at 25 °C. Entropies of activation for cyclohexanone, benzaldehyde, 2-methylpropanal, and 2,2-dimethylpropanal are positive, and enthalpy–entropy compensation is observed. Effects of cycloalkane ring size and benzaldehyde substituents are small and are ascribable to a transition state with a very small C–C bond order. A two-step mechanism is proposed, with preequilibrium formation of a coordination intermediate which, in some cases, is accompanied by a change in the magnesium coordination number. Effects of alkyl groups on aldehyde and ketone reactivity stem mainly from steric desolvation.

Enediolates of carboxylic acids 1, known as Ivanov reagents, are usually obtained by the action of an or-

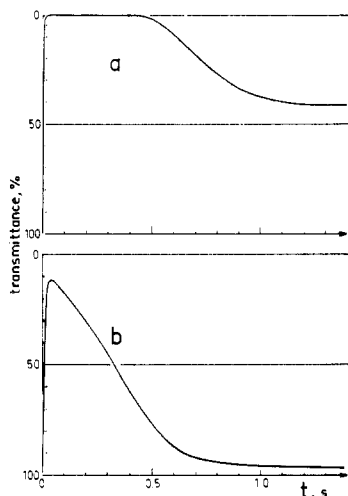
ganometallic reagent on carboxylic acids RCH<sub>2</sub>COOH.<sup>3,4a,b</sup> Reactions of Ivanov reagents with electrophiles such as

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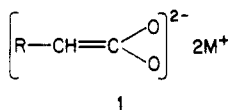
<sup>§</sup> Université Pierre-et-Marie Curie.

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**Figure 1.** Typical stopped-flow transmittance vs. time curves observed after mixing equal amounts of the Ivanov reagent (0.0452 M) and cyclohexanone (0.804 M) solutions (curve a,  $\lambda$  310 nm; curve b,  $\lambda$  345 nm).

carbonyl compounds (Ivanov reaction) have been reviewed.<sup>4</sup>



Recent <sup>1</sup>H NMR spectroscopy data on the magnesium enediolate of phenylacetic acid in THF,<sup>5</sup> as well as stereochemical studies of its reaction with 4-*tert*-butylcyclohexanone,<sup>6</sup> show that this reagent reacts as an enolate and that molecular associations seemingly do not occur. Previous investigations of the mechanism of the Ivanov and similar reactions of carbonyl compounds have been essentially confined to product studies, primarily stereochemical.<sup>6-11</sup> The Ivanov reaction yields mixtures of threo

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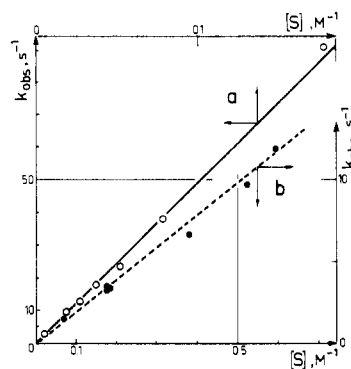
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**Figure 2.** Apparent first-order rate constants (25 °C) vs. 2-methylpropanal (curve a) and cyclohexanone (curve b) concentrations.

and erythro diastereoisomers, usually with a slight predominance of the threo product. Two explanations for this result have been advanced: (i) The transition-state geometry is imposed by stereoelectronic requirements (perpendicular attack)<sup>12</sup> and by metal ion bridging between one of the enediolate oxygen atoms and the carbonyl oxygen atom. (ii) The transition state owes its geometry to a 1,3-dipolar cycloaddition-like interaction between frontier orbitals.<sup>11</sup>

We here report on a kinetic study of the fast reaction of 1 (R = Ph, M = 1/2 Mg) with various aldehydes and ketones and discuss entropies of activation, effects of structure on rate constants, and the reaction mechanism.

## Results

Dilute solutions of 1 prepared by mixing phenylacetic acid with isopropylmagnesium chloride exhibit strong absorptivity at  $\sim 305$  nm ( $\lambda_{\text{max}}$  307 nm,  $\epsilon \sim 10^4$  M<sup>-1</sup> cm<sup>-1</sup>). Typical stopped-flow kinetic runs of 1 with a carbonyl compound, measured at 310 and 345 nm, are shown in Figure 1. Because of the high absorbance of 1 at 310 nm, it was possible to follow only the last 4-8% of the reaction, from a concentration of  $\sim 10^{-3}$  M. In contrast, transmittance-time curves at 345 nm correspond to the overall magnesium enediolate uptake from  $\sim 2 \times 10^{-2}$  M.

**Kinetic Law.** For measurements at 305-310 nm, ketone or aldehyde concentrations at least 10 times that of the enediolate dianion were chosen so that pseudo-first-order conditions would be valid for the last part of the reaction. Under these conditions, absorbance variations fit a Guggenheim-transformed first-order equation (eq 1),

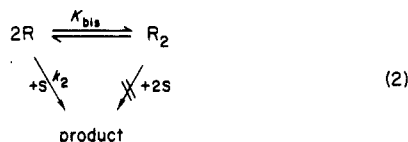
$$A_t - A_{t'} = (A_1 - A_\infty)(1 - e^{-k_{\text{obs}}\theta})e^{-k_{\text{obs}}t} \quad (1)$$

where  $A_t$  and  $A_{t'}$  are the absorbances at times  $t$  and  $t'$  separated by a constant time interval  $\theta$ .  $A_1$  is the absorbance at the arbitrary first point, and  $A_\infty$  is the asymptotic absorbance calculated from the intercept of the linear plot of  $\ln(A_t - A_{t'})$  vs.  $t$ . For cyclohexanone, cyclopentanone, cyclobutanone, and most aldehydes,  $A_\infty$  was approximately the absorbance calculated at the end of the reaction by taking into account the excess carbonyl compound absorption. In these cases, the reaction was considered complete, so  $k_{\text{obs}}$  corresponded to the forward reaction. With acetone, acetophenone, and cycloheptanone, the  $k_{\text{obs}}$  values include a small contribution from the reverse reaction, deduced as negligible on the basis of estimated equilibrium constants. With 3-pentanone and cyclooctanone, reversibility was sufficient that kinetic measurements could not be performed at 305-310 nm.

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Values of  $k_{\text{obsd}}$  measured at different concentrations of the carbonyl compound gave the zero intercept straight lines in Figure 2, indicating a second-order reaction for enediolate dianion concentrations  $<10^{-3}$  M.

For higher enediolate concentrations, measured at longer wavelengths, the  $A_t$  curves indicate a lower rate than that calculated from the second-order law. We assume that at higher enediolate concentrations a relatively unreactive species containing two enolate ions ( $R_2$ ) is formed (eq 2). With the carbonyl compound (S) in large excess and the reaction equilibrium far to the right, eq 3 can be derived. Here,  $[R]_{\text{st}} (= 2[R_2] + [R])$  is the stoichiometric concentration of enediolate ion. Integration of eq 3 yields eq 4, where  $C$  is the value of the left-hand term for the arbitrary first point ( $t = t_1$ ).



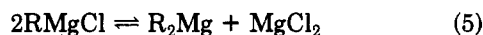
$$-d[R]_{\text{st}}/dt = k_2[S]((1 + 8K_{\text{bis}}[R]_{\text{st}})^{1/2} - 1)/4K_{\text{bis}} \quad (3)$$

$$(1 + 8K_{\text{bis}}[R]_{\text{st}})^{1/2} + \ln((1 + 8K_{\text{bis}}[R]_{\text{st}})^{1/2} - 1) = -k_2[S](t - t_1) + C \quad (4)$$

Although enediolate concentrations could not be calculated at 305–310 nm because of the high absorptivity of the Ivanov reagent, stoichiometric concentrations were calculated for cyclohexanone for each point of the transmittance–time curves at 345 nm. Apparent extinction coefficients were measured, assuming that the absorptivity of the enediolate ion in R was identical to that in  $R_2$ .<sup>13</sup> Equation 4 was tested by repetitive calculations with different  $K_{\text{bis}}$  values and with  $k_2$  values from kinetic runs at 305–310 nm. A good fit of the experimental curve to eq 4 was found with  $K_{\text{bis}} = 60 \pm 10 \text{ M}^{-1}$ , indicating that formation of an unreactive bis(enediolate) is consistent with kinetic data at concentrations greater than  $10^{-3}$  M.

The first-order equation followed at low enediolate concentrations is a limiting form of eq 3. First-order behavior should occur when the term  $((1 + 8K_{\text{bis}}[R]_{\text{st}})^{1/2} - 1)$  is roughly equal to  $4K_{\text{bis}}[R]_{\text{st}}$ . Taking  $K_{\text{bis}} = 60 \text{ M}^{-1}$  the ratio  $((1 + 8K_{\text{bis}}[R]_{\text{st}})^{1/2} - 1)/4K_{\text{bis}}[R]_{\text{st}}$  will not exceed 1.1 for  $[R]_{\text{st}} < 10^{-3}$  M and the error in the first-order approximation will not exceed 3%, which we neglect.

Studies on Grignard reagents have shown that the Schlenk equilibrium (eq 5) results in the formation of  $\text{MgCl}_2$  in THF<sup>14</sup> and that adding  $\text{MgCl}_2$  decreases the ratio  $[\text{R}_2\text{Mg}]/[\text{RMgCl}]$ . However, addition of 0.1 M  $\text{MgCl}_2$  to



the Ivanov reagent ( $[\text{R}]_{\text{st}} = 2 \times 10^{-2}$  M) produced no significant changes in  $k_2$  ( $21.8 \text{ M}^{-1} \text{ s}^{-1}$  instead of  $18.2 \text{ M}^{-1} \text{ s}^{-1}$  without  $\text{MgCl}_2$ ) and  $K_{\text{bis}}$ .

Equations 3 and 4 are not valid when significant reversibility occurs (3-pentanone and cyclooctanone), and in this case eq 3 should be replaced by eq 6, where  $k_{-1}$  is the reverse first-order rate constant and  $[P]$  is the product concentration at time  $t$ . Since integration of eq 6 is not straightforward, we used a numerical integration technique (trapezoidal rule) with the integrated equation expressed

Table I. Second-Order Rate Constants for the Reaction of Carbonyl Compounds with 1 and Estimated Equilibrium Constants (in THF, 25 °C)<sup>a</sup>

carbonyl compound	$k_2$ , <sup>b</sup> $\text{M}^{-1} \text{ s}^{-1}$	$K$ , $\text{M}^{-1}$
3-chlorobenzaldehyde	766 ± 23	
4-chlorobenzaldehyde	646 ± 21	
benzaldehyde	561 ± 30	
3-methylbenzaldehyde	400 ± 30	
4-methylbenzaldehyde	307 ± 32	
4-methoxybenzaldehyde	215 ± 4	
propanal	670 <sup>c</sup>	
2-methylpropanal	465 ± 27	
2,2-dimethylpropanal	74 ± 3	
cyclobutanone	25.1 ± 1.5	
cyclopentanone	16.2 ± 1.5	
cyclohexanone	19.4 ± 1.0	
cycloheptanone	10.7 ± 1.0	
cyclooctanone	3.0 ± 0.5	13
acetophenone	5.1 ± 0.5	400
acetone	13.4 ± 1.1	>2000
3-pentanone	0.95 ± 0.10	15

<sup>a</sup> ±0.1 °C. <sup>b</sup> Errors are standard deviations. <sup>c</sup> Calculated from data at 5 °C ( $k_2 = 125 \text{ M}^{-1} \text{ s}^{-1}$ ), by assuming that  $\Delta H^\ddagger = 13.8 \text{ kcal mol}^{-1}$  as observed for 2-methylpropanal.

as eq 7, where  $[\text{R}]_{\text{st}}^i$  is the initial concentration of the enediolate reagent and  $K$  is the estimated equilibrium constant of the Ivanov reaction. This equation was shown to be valid with  $K_{\text{bis}} = 60 \text{ M}^{-1}$ . The pseudo-first-order rate constants ( $k_2[S]$ ) for the forward reaction were calculated as the slopes of the linear plots of the left-hand term vs. the numerically calculated integral.

$$-\frac{d[\text{R}]_{\text{st}}}{dt} = k_2[S] \left[ \frac{(1 + 8K_{\text{bis}}[\text{R}]_{\text{st}})^{1/2} - 1}{4K_{\text{bis}}} \right] - k_{-1}[P] \quad (6)$$

$$([\text{R}]_{\text{st}})_t - ([\text{R}]_{\text{st}})_t = k_2[S] \int_t^t \left[ \frac{(1 + 8K_{\text{bis}}[\text{R}]_{\text{st}})^{1/2} - 1}{4K_{\text{bis}}} + \frac{[\text{R}]_{\text{st}}}{K[\text{S}]} \right] dt - k_{-1}[\text{R}]_{\text{st}}^{i\theta} \quad (7)$$

The second-order rate constants for a number of carbonyl compounds at 25 °C are listed in Table I. Values of  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  were calculated by plotting  $\ln(k_2/T)$  vs.  $1/T$  [ $k_2$  expressed in temperature independent concentration units (M at 25 °C)]<sup>15</sup> (Table II).

## Discussion

**Structure of the Ivanov Reagent.** The <sup>1</sup>H NMR spectrum of 1 is similar to that of  $\text{PhCH}=\text{C}(\text{OSiMe}_3)_2$ .<sup>5</sup> Singlet peaks at 4.26 and 4.68 ppm are ascribed to the vinyl proton and indicate an enolate (O-metalated) form of the Ivanov reagent rather than a C-metalated form.<sup>5</sup> The stereochemistry of the Ivanov reaction with 4-*tert*-butylcyclohexanone supports the hypothesis that the reactive species are the enediolates observed by NMR spectroscopy.<sup>6</sup>

The same threo/erythro product ratio (60:40) is obtained in the reaction of benzaldehyde with Ivanov reagents formed in different ways ( $\text{PhCH}_2\text{COONa} + i\text{-PrMgBr}$ ,  $\text{PhCH}_2\text{COOMgBr} + \text{naphthyl Na}$ ,  $\text{PhCH}_2\text{COOH} + 2i\text{-PrMgBr}$ ,  $\text{PhCHBrCOOMgBr} + \text{Mg}$ ) when one of the cations is Mg and the other is Mg or Na.<sup>10b,c</sup> On the other hand, when the two cations are sodium, lithium, or zinc ( $\text{PhCH}_2\text{COOH} + 2\text{Naphthyl Na}$ ,  $\text{PhCH}_2\text{COOH} +$

(13) By analogy to metal acetylacetonates, in which  $\epsilon$  and  $\lambda_{\text{max}}$  are essentially independent of the counterion (Holm, R. H.; Cotton, F. A. *J. Am. Chem. Soc.* 1958, 80, 5658–5663. See also: DePalm, V. M.; Arnett, E. M. *J. Am. Chem. Soc.* 1978, 100, 3514–3525).

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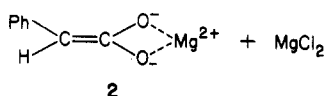
(15) Slightly different  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  values are reported in ref 2. These were obtained from  $k_2$  data expressed in concentration units at the temperature of the experiment.

Table II. Activation Parameters

carbonyl compound	$\Delta G^*_{298}$ , kcal mol <sup>-1</sup>	$\Delta H^*$ , kcal mol <sup>-1a</sup>	$\Delta S^*$ , cal mol <sup>-1</sup> K <sup>-1a</sup>
2-methylpropanal	13.81	13.85 ± 0.20 <sup>b</sup>	0.2 ± 0.7 <sup>b</sup>
2,2-dimethylpropanal	14.88	18.00 ± 0.70 <sup>c</sup>	10.5 ± 2.0 <sup>c</sup>
benzaldehyde	13.68	16.95 ± 0.20 <sup>d</sup>	11.0 ± 0.7 <sup>d</sup>
cyclohexanone	15.68	21.15 ± 0.50 <sup>e</sup>	18.4 ± 1.0 <sup>e</sup>

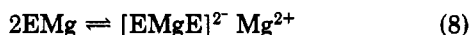
<sup>a</sup> Error limits estimated from uncertainties in second-order rate constants. <sup>b</sup> From data at 5, 10, 20, 25, and 30 °C. <sup>c</sup> From data at 10, 20, 25, and 30 °C. <sup>d</sup> From data at 5, 20, 25, and 30 °C. <sup>e</sup> From data at 10, 20, 25, 30, and 40 °C.

2Naphthyl Li, PhCHBrCOOZnBr + Zn) or when one of the cations is zinc (PhCHBrCOOZnBr + Mg), the threo/erythro ratios are very different.<sup>16</sup> To rationalize these results it has been suggested<sup>10c</sup> that the Ivanov reagent is a magnesium enediolate rather than a sodium/bromomagnesium enediolate when the counterions are magnesium and sodium. If so, the Ivanov reagent used in this work can be described as 2. However, by analogy with



Grignard reagents in THF,<sup>14,17</sup> strong solvation by THF molecules should occur. Since magnesium ions can coordinate four, five, or six ligands, depending on the ligands,<sup>18</sup> there can be as many as four THF molecules in the first ligand sphere. As seen below, strong desolvation during the reaction accounts for the large positive  $\Delta S^*$ , and solvation by four THF molecules seems most likely.

The bis(enediolate)  $R_2$  cannot be formed by disproportionation of a bis(chloromagnesium) species since that reaction would produce  $MgCl_2$ , and a significant  $MgCl_2$  effect on  $K_{bis}$  would have been observed. On the other hand, the bis(enediolate) can result from complexation of magnesium by two enediolate ions (E) (eq 8) to yield an ion pair, with  $MgCl_2$  in balance on both sides of the equilibrium.



At first sight, the conclusion that a bis(enediolate) is the predominant form in moderately concentrated solutions is inconsistent with the absence of spectral changes when lowering the temperature to -40 °C or adding up to 20% HPMT (this has been interpreted as ruling out molecular association).<sup>5</sup> However, the NMR spectrum of symmetrically bonded enediolates in a bis(enediolate) should not be very different from that of a mono(enediolate). What is certain is that conglomerates do not form.

**Enthalpies and Entropies of Activation.** The observation of positive entropies of activation, some of which are large, is significant. A large positive entropy of activation usually reflects an increase in the number of translational degrees of freedom on going from the reactants to the transition state<sup>19</sup> and is often found in reactions that increase the number of chemical species. It follows that the  $\Delta S^*$  of 18.4 cal mol<sup>-1</sup> K<sup>-1</sup> observed for the addition of cyclohexanone to the enediolate ion is inconsistent with a simple bimolecular process.

Since the addition of carbonyl compounds to metal enediolates forms a chelated product in which the ion is bonded to the alcoholate oxygen atom and to the carboxy group, the sequence of C-C and O-Mg bond formations

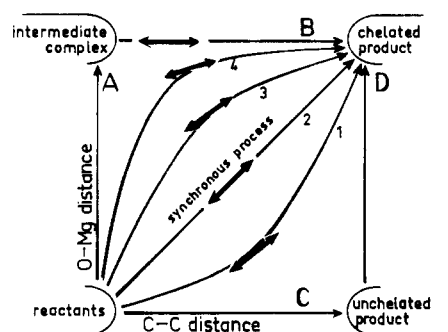
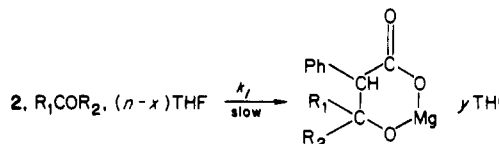
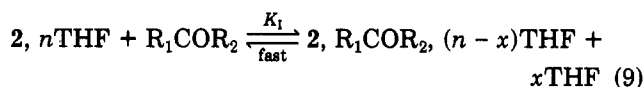


Figure 3. Schematic potential energy surface for the Ivanov reaction.

should follow one of the possible schematic potential energy surfaces of the reaction depicted in Figure 3:<sup>20</sup> (i) a stepwise mechanism following processes A (complexation) and B (C-C bond formation), (ii) a stepwise mechanism with rate-limiting C-C bond formation in the first step (C) followed by chelation (D), or (iii) a concerted mechanism (paths 1-4) involving concerted formation of the C-C and O-Mg bonds.

Hypothesis ii, which is analogous to that of Muzler et al.<sup>11b,c</sup> based on stereochemical data, is not in keeping with the observed positive entropies of activation. Such a process should have negative entropies of activation.

Mechanism i is analogous to that observed in the Grignard reaction:<sup>14</sup> complex formation, due to replacement of a liganded solvent molecule by the carbonyl compound, promotes a metal-assisted intramolecular attachment of the enediolate anion to the carbonyl compound. Such a mechanism, which can be described by eq 9 taking  $x = 1$ , would be in agreement with the near-zero  $\Delta S^*$  observed for 2-methylpropanal, assuming that the entropy of activation for the rate-limiting step is negligible. However, when  $\Delta S^*$  is very positive, preequilibrium complexation must also be accompanied by the loss of more than one THF molecule.



Large  $\Delta S^\circ$  values for the disproportionation equilibrium of Grignard reagents in THF have been interpreted in terms of changes in solvation numbers in going from  $MgBr_2, 4\text{THF}$  to  $\text{EtMgBr}, 2\text{THF}$ .<sup>14,17</sup> The observed  $\Delta S^\circ$  of 23.7 cal mol<sup>-1</sup> K<sup>-1</sup> has been ascribed to an increase in the number of translational degrees of freedom associated

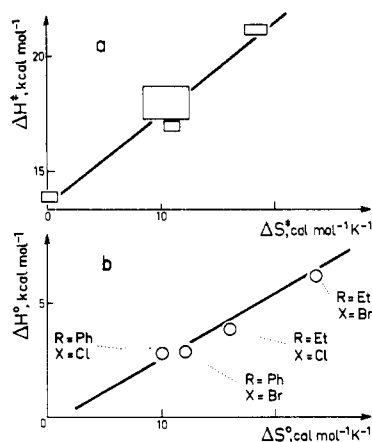
(16) See also: Bellasoued, M.; Gaudemar, M. *J. Organometal. Chem.* 1975, 102, 1-5.

(17) Smith, M. B.; Becker, W. E. *Tetrahedron* 1967, 23, 4215-4227.

(18) See for example: Purcell, K. F.; Katz, J. C. "Inorganic Chemistry"; Saunders: Philadelphia, 1977; pp 850-852.

(19) Schaleger, L. L.; Long, F. A. *Adv. Phys. Org. Chem.* 1963, 1, 1-33.

(20) More O'Ferrall, R. A. *J. Chem. Soc. B* 1970, 274-277. Jencks, W. P. *Chem. Rev.* 1972, 72, 705-718. Albery, W. J.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* 1978, 16, 87-157. Jencks, W. P. *Chem. Soc. Rev.* 1981, 10, 345-375. Jencks, W. P. *Acc. Chem. Res.* 1980, 13, 161-169.



**Figure 4.**  $\Delta H^\ddagger - \Delta S^\ddagger$  relationship for the Ivanov reaction (data from Table II, curve a) and  $\Delta H^\circ - \Delta S^\circ$  relationship for the disproportionation of Grignard reagents in THF (data from ref 17)(curve b).

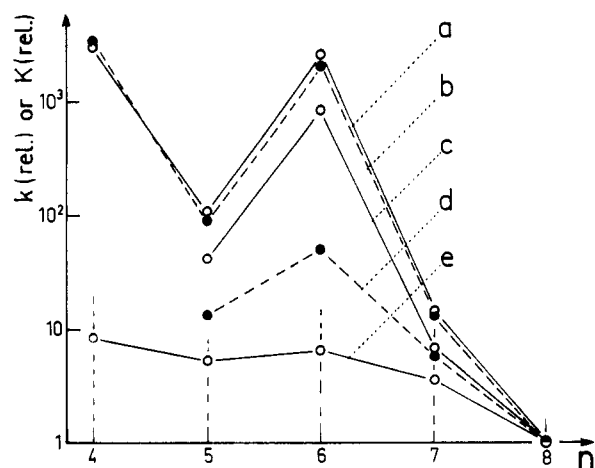
with 2 mol of THF, and the entropy change per mole of THF (23.7/2) is close to the molar entropy of melting at 25 °C. Comparison of  $\Delta S^\circ$  for the disproportionation equilibrium with  $\Delta S^\ddagger$  for the Ivanov reaction of cyclohexanone suggests that as many as three THF molecules are released in the complexation of the carbonyl compound, involving an increase of two in the number of chemical species, and that Mg(II) undergoes a change in coordination number (probably from 6 to 4).

The data in Table II show that  $\Delta S^\ddagger$  decreases when reactivity increases and approaches zero for 2-methylpropanal. Since the variations in  $\Delta G^\ddagger$  with structure are relatively small, the  $\Delta S^\ddagger$  decrease is accompanied by a large  $\Delta H^\ddagger$  decrease, i.e., partial enthalpy-entropy compensation. This effect is depicted by a rough  $\Delta H^\ddagger - \Delta S^\ddagger$  isokinetic relationship (Figure 4) with an isokinetic temperature of  $\sim 390$  K.<sup>21</sup>

Enthalpy-entropy compensation is common when variations in  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  with structure are due to solute-solvent interactions.<sup>22</sup> It is also observed in ligand exchange equilibria when a ligand replaces  $x$  liganded solvent molecules. For example, it has been observed in disproportionation equilibria of Grignard reagents in THF with different R groups and/or halide ions<sup>17</sup> (Figure 4). The slope and the range in  $\Delta S^\circ$  and  $\Delta S^\ddagger$  stem from the same factor, namely THF desolvation.

It follows that the  $\Delta S^\ddagger$  values for the Ivanov reaction can be interpreted by assuming the validity of hypothesis i (eq 9) and the dependence of  $x$  on the carbonyl compound. However, since a positive  $\Delta S^\ddagger$  is only characteristic of magnesium desolvation, a concerted mechanism (hypothesis iii) cannot be strictly excluded. If the latter mechanism were valid, the large and positive  $\Delta S^\ddagger$  values observed would require a degree of desolvation comparable to that expected for the two-step mechanism.

**Cycloalkanone Reactivity: Ring-Size Effects.** A reaction that results in the  $sp^2 \rightarrow sp^3$  hybridization change of an endocyclic carbon atom usually depends on the strain energy difference ( $\Delta SI$ ) between  $sp^2$  and  $sp^3$  hybridization states.<sup>23</sup> When this effect prevails, the relationship between  $\Delta H^\ddagger$  and  $\Delta SI$  indicates the degree of the trigonal-to-tetrahedral geometry change at the transition state. The



**Figure 5.** Ring size effects on rate constants for the Ivanov reaction with cycloalkanones ( $C_nH_{2n-2}O$ ) and for reactions involving a similar  $sp^2$  to  $sp^3$  hybridization change of the endocyclic carbonyl carbon atom. (a) Dimethyl acetal equilibrium constants.<sup>26</sup> (b) Rate constants for reduction by  $NaBH_4$ .<sup>27</sup> (c) Cyanohydrin equilibrium constants.<sup>24</sup> (d) Rate constants for reduction by 9-borabicyclo[3.3.1]nonane dimer (see ref 28). (e) Rate constants for the Ivanov reaction (data from Table I). Constants are relative to cyclooctanone.

slope is close to unity when plotting  $\Delta G^\circ$  vs.  $\Delta SI$  for equilibria<sup>24-26</sup> or  $\Delta G^\ddagger$  vs.  $\Delta SI$  for rate data when the transition state is product-like (as for  $NaBH_4$  reduction<sup>27</sup>), whereas it should be close to zero for reactions with very early transition states. In Figure 5, variations in  $k_2$  with ring size for the Ivanov reaction are compared to those of equilibrium or rate constants for reactions controlled by strain effects; although the same trend is observed, the relative variations with ring size are much smaller.<sup>28</sup> The slope ( $\approx 0.15$ ) of the plot of  $\Delta G^\ddagger$  against  $\Delta SI$  is characteristic of very small C-C bond formation at the transition state.<sup>29</sup>

If assistance by the metal ion is not considered, such a very early transition state would be inconsistent with a one-step mechanism. According to the Leffler-Hammond postulate,<sup>30</sup> a one-step mechanism associated with a large enthalpy of activation should involve a large geometry change from the carbonyl compound to the transition state. In contrast, the two-step mechanism (eq 9) would apply because most of the enthalpy of activation would be due to THF desolvation in the preequilibrium step. Therefore, the small C-C bond order at the transition state would stem from the small enthalpy of activation for the rate-limiting step and from its large positive  $\Delta H^\circ$  value.

Notwithstanding, a two-step mechanism is not strictly required to explain the small C-C bond formation at the transition state; a concerted mechanism with large O-Mg bond formation and small C-C bond formation is another plausible possibility (Figure 3). Recent studies<sup>20</sup> have shown that the transition state of a concerted reaction can

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(28) Cycloalkanone reduction by 9-borabicyclo[3.3.1]nonane dimer has a transition state less product-like than that of reduction by  $NaBH_4$  (Brown, H. C.; Wang, K. K.; Chandrasekharan, J. *J. Am. Chem. Soc.* 1983, 105, 2340-2343. The plot of  $\Delta G^\ddagger$  vs.  $\Delta SI$  is linear with a slope of ca. 0.60.

(29) The point for cyclooctanone deviates from the linear relationship between  $\Delta G^\ddagger$  and  $\Delta SI$ , probably as due to steric effects as observed for aliphatic ketones. The 0.15 slope is that calculated when this point is discarded.

(30) Hammond, G. S. *J. Am. Chem. Soc.* 1955, 77, 334-338.

(21) Statistical treatment of the  $\Delta H^\ddagger - \Delta S^\ddagger$  relationship (ref 22) was not used for only four sets of values.

(22) For a review, see: Exner, O. *Prog. Phys. Org. Chem.* 1973, 10, 411-482.

(23) Schneider, H. J.; Schmidt, G.; Thomas, F. *J. Am. Chem. Soc.* 1983, 105, 3556-3563.

resemble the potential reaction intermediate when the latter is fairly stable but does not have a sufficiently long lifetime to allow the stepwise mechanism to occur. Accordingly, the Ivanov reaction can be concerted with a transition state resembling the intermediate complex and only slight C-C bond formation and large O-Mg bond formation.

**Reactivity of Benzaldehydes: Ring-Substituent Effects.** When second-order rate constants are plotted vs. Wepster<sup>31</sup>  $\sigma^n$  and Brown-Okamoto<sup>32</sup>  $\sigma^+$  substituent parameters, a better relationship is observed with  $\sigma^+$ . The slope is 0.54 ( $r = 0.97$ ). This relationship resembles that for nucleophilic attachments to the carbonyl group of benzaldehydes or acetophenones: rate constants and equilibrium constants correlate with  $\sigma^+$  (or the Yukawa-Tsuno equation)<sup>33</sup> because of polar effects and the loss of through-ring conjugation on going from the carbonyl compound to the product or the transition state. However, the  $\rho$  value is fairly small compared to values observed for other reactions.<sup>34,35</sup> Therefore, since the  $\rho$  value can be related to the change in hybridization character of the carbonyl carbon atom on going from the initial state to the transition state,<sup>36</sup> the small ring substituent effects are in agreement with a small C-C bond order.

**Steric Desolvation.** Data in Table I show that the second-order rate constant,  $k_2$ , decreases slightly on going from propanal to 2-methylpropanal to 2,2-dimethylpropanal. Although it is difficult to dissect polar, hyperconjugative, and steric effects, it seems likely that this decrease reflects a weak steric effect. Moreover, a comparison of data for acetone and 3-pentanone indicates that the reaction rate is depressed by steric effects of the larger groups around the carbonyl group.

The large difference between aldehyde and ketone reactivities is also probably due in part to steric effects. The ratio between  $k_2$  values for benzaldehyde and acetophenone, or between  $k_2$  values for propanal and acetone (110 and 50, respectively), is larger than expected from the very small C-C bond formation at the transition state. The smaller reactivities of ketones vs. aldehydes for nucleophilic additions to the carbonyl group are primarily due to the hyperconjugative stabilization of the carbonyl compounds by the additional alkyl group.

Since variations in  $\Delta S^\ddagger$  are believed to be closely related to magnesium ion desolvation, it seems clear that steric desolvation is the main factor behind the overall steric effect. More quantitatively, the rate constant  $k_2$  can be expressed as

$$k_2 = k_1 K_1 / [\text{THF}]^x$$

assuming that the two-step mechanism (eq 9) is valid. Therefore, the ratio of 2-methylpropanal and 2,2-dimethylpropanal rate constants ( $\sim 6$ ) can be ascribed to a difference in  $x$  of 0.7, which is in agreement with the entropy data.

(31) Van Bekkum, H.; Verkade, P. E.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* 1959, 78, 815-850.

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(33) Jencks, W. P. *Prog. Phys. Org. Chem.* 1964, 2, 63-128.

(34) Toullec, J.; El-Alaoui, M.; Kleffert, P. *J. Org. Chem.* 1983, 48, 4808-4816.

(35) Arota, M.; Cox, B. G.; Sørensen, P. E. *J. Chem. Soc., Perkin Trans. 2* 1979, 103-107.

(36) Values of  $\rho$  for rate constants of uncatalyzed nucleophilic addition to the carbonyl group depend on the degree of resemblance of the transition state to the product. When the transition state is early,  $\rho$  is low because there are similar inductive and resonance effects on the energies of the transition state and starting materials; when it is late, the  $\rho$  values are large and close to those observed on equilibria (2-3.5).

**Stereoselectivity and Mechanism.** The stereoselectivity of the Ivanov reaction with different metallic enediolates is usually very low<sup>9-11</sup> and in the opposite direction from that expected from the abilities of the cations to promote bidentate chelation.<sup>11b,c</sup> The predominance of the threo isomer from aldehydes is usually explained by the "bridging" effect of the metal ion, which imposes a syn configuration on the transition state.<sup>9</sup> The small degree of C-C bond formation at the transition state can explain the low kinetic stereoselectivity for magnesium enediolates and the large differences in threo/erythro ratios usually observed between kinetic control and equilibrium control.<sup>11a,c</sup> Thus the distance between carbon atoms is sufficiently large that nonbonding interactions are of minor importance.

It seems likely that the two-step mechanism described by eq 9 is not valid when the ability of the cation to be liganded decreases because the lifetime of the potential reaction intermediate is too short. So it is likely that a concerted mechanism is to be preferred for sodium or potassium enediolates, alone or chelated by cryptands or crown ethers. Examination of the schematic potential energy surfaces (Figure 3) indicates that a decrease in the stability of the potential reaction intermediate should make the transition state less similar to the intermediate, i.e., with the O-M bond less formed and the C-C bond more formed. It follows that the perpendicular effect should make the C-C bond order closer to unity for cations with little ability to form chelates. This would explain the enhancement of the factors favoring threo isomer formation, and the variations in stereoselectivity when changing the counterion should not be considered abnormal.

## Conclusion

Entropy data and effects of carbonyl compound structure are consistent with a two-step mechanism with prior association of the carbonyl compound with magnesium ion. Although the data do not strictly rule out a concerted mechanism, they clearly indicate that the transition state is very intermediate-like and corresponds to a very small C-C bond formation. Thus the magnesium ion provides strong electrophilic assistance and constitutes a template for the reactants.

## Experimental Section

**Materials.** THF was distilled from  $\text{LiAlH}_4$  in an inert atmosphere just prior to use. Carbonyl compounds were distilled (aldehydes under nitrogen and just prior to use). Solutions in THF were prepared in a drybox under nitrogen. Ivanov reagent solutions at stoichiometric concentrations of ca.  $5 \times 10^{-2}$  M were prepared as follows. To 0.370 g (2.5 mmol) of phenylacetic acid (recrystallized and dried) was added 5.5 mmol of isopropylmagnesium chloride (solution in THF, titrated just prior to use with a 1 M solution of 2-methylpropanol in xylene; indicator *o*-phenanthroline). After 1 h at room temperature, the mixture was brought to 50 mL by adding THF. To ensure that the observed rate constants were independent of the small excess of isopropylmagnesium chloride, Ivanov reagent solutions were prepared by adding either 6.3 or 7.65 mmol of isopropylmagnesium chloride; instead of the 5 mmol required for total conversion of phenylacetic acid. The absence of product concentration influence was checked with a solution prepared by the successive addition of 11 mmol of isopropylmagnesium chloride and 2.5 mmol of cyclohexanone to phenylacetic acid (5 mmol); THF was added to bring the mixture to 50 mL.

**Reaction of the Ivanov Reagent with Cyclohexanone and Cyclooctanone.** Since stopped-flow kinetic measurements require that the Ivanov reagent react quickly and that no side reaction occurs, the reagent was added to cyclohexanone at room temperature under conditions analogous to those used for kinetic experiments. Equal volumes (10 mL) of the Ivanov reagent

(prepared as described above, but 0.1 M) and of cyclohexanone (0.4 M in THF) were mixed rapidly in a conical flask under nitrogen. The mixture was rapidly hydrolyzed by acidic water (about 2 s after mixing). The reaction product was extracted with diethyl ether, recrystallized, and identified as 2-(1-hydroxycyclohexyl)-2-phenylacetic acid: mp 139 °C (lit. mp 135 °C<sup>3a</sup>); yield 99%. The same result was obtained when the mixture was allowed to react for 5 min after mixing. Similar experiments were performed by using 10 mL of cyclohexanone solution (1.96 M) and 60 mL of Ivanov reagent (0.33 M). The mixture was allowed to react for 2 min at 25 °C before hydrolysis. The yield was 68%, indicating an incomplete reaction (no side reaction). From these data an equilibrium constant of 24 M was calculated, in fair agreement with that estimated from the asymptotic values of transmittance at the end of the kinetic runs.

**Kinetic Measurements.** Kinetic measurements were performed with an SF-3A Canterbury Stopped-Flow Spectrophotometer (Nortech Laboratories, UK) (optical path = 0.2 cm) equipped with an SFD-2S Variable Ratio Drive Unit and a memory oscilloscope (Hewlett-Packard, 5480A Memory/display), recording the voltage-time curve on a Servotrace recorder (PE Model, Sefram, France). Solutions of cyclohexanone and of the magnesium enediolate in the two reservoirs were shielded from oxygen and moisture by an argon stream. For enediolate titration, aliquots (5 mL) of Ivanov reagent solution were transferred to an argon-filled flask containing 100  $\mu$ L of DCl/D<sub>2</sub>O. Points on the voltage-time curve were converted to transmittances and to absorbances by taking into account oscilloscope-measured voltages for full (concentrated enediolate reagent solutions) and zero (THF only) absorbances. For data at 305–310 nm, least-squares Guggenheim plots were constructed to obtain pseudo-first-order rate constants. At 345 nm, apparent extinction coefficients ( $\epsilon \approx 300$  M<sup>-1</sup> cm<sup>-1</sup>) were measured before the run from the transmittance data for the initial magnesium enediolate solution and for reagent/THF mixtures obtained by the variable ratio drive unit. Concentration-time curves were calculated with the Lambert-Beer equation, whatever the species in the solution [mono(enediolate) or bis(enediolate)].<sup>13</sup> Equation 4 was tested on a Vax 11 computer (Digital Equipment Corp.) with a Fortran program designed for the calculation of  $k_2$  for a large set of  $K_{bis}$  values (typically between 40 and 100 M<sup>-1</sup>) by a least-squares treatment.  $K_{bis}$  was calculated as the abscissa of the cross point between the plot of  $k_2$  vs.  $K_{bis}$  and the horizontal line corresponding to the  $k_2$  value measured at low concentration (305–310 nm). Usually, this  $K_{bis}$  corresponded

to the largest value of  $Z$  (normal variate),<sup>37</sup> but not necessarily to the largest correlation coefficient, always larger than 0.9995.

The small excess (ca. 10%) of isopropylmagnesium chloride did not introduce errors. Kinetic measurements performed with a larger excess of Grignard reagent (ca. 20% and 50%, respectively) gave  $k_2$  values of 18.3 and 21.3 M<sup>-1</sup> s<sup>-1</sup>, whereas under the same conditions, the normal value (with 10% excess) was  $k_2 = 18.3$  M<sup>-1</sup> s<sup>-1</sup>. An enediolate solution containing an amount of preformed reaction product equal to that formed during the run yielded similar results ( $k_2 = 18.4$  M<sup>-1</sup> s<sup>-1</sup>).

**Enediolate Determination in the Ivanov Reagent.** The procedure was based on the conversion of magnesium enediolate into 2-*d*-phenylacetic acid by the action of DCl/D<sub>2</sub>O and on mass spectroscopy determination of the relative proportions of PhCHDCOOH and PhCH<sub>2</sub>COOH (the latter compound was formed by partial hydrolysis from slight moisture contamination during the kinetic procedure). To 5 mL of the Ivanov reagent was added 100  $\mu$ L of a solution of DCl (20%) in D<sub>2</sub>O (%D > 99%) (Gold Label, Aldrich). THF was removed under vacuum. HCl (1 mL) was then added and the product was extracted with diethyl ether. After the organic layer had been washed with a saturated solution of NaCl, it was separated and dried with magnesium sulfate. The solvent was removed under vacuum. The resulting material was dissolved in CCl<sub>4</sub> (0.4 mL) and analyzed by mass spectroscopy (75 eV, JEOL JMS 200 spectrometer connected to a JEOL Gas 20K GLO and to a JEOL mass data system computer). The relative peak intensities  $m/e$  91 and 92 (corresponding mainly to PhCH<sub>2</sub><sup>+</sup> and to PhCHD<sup>+</sup>, respectively) were used to determine molar fractions of PhCH<sub>2</sub>COOH and PhCHDCOOH from the equation

$$\% \text{ PhCH}_2\text{COOH} = 100[1 - 1.084h_{91}/1.084(h_{92} - 0.084h_{91})]$$

**Registry No.** PhCH<sub>2</sub>CO<sub>2</sub>H, 103-82-2; *i*-PrMgCl, 1068-55-9; *m*-ClC<sub>6</sub>H<sub>4</sub>CHO, 587-04-2; *p*-ClC<sub>6</sub>H<sub>4</sub>CHO, 104-88-1; PhCHO, 100-52-7; *m*-MeC<sub>6</sub>H<sub>4</sub>CHO, 620-23-5; *p*-MeC<sub>6</sub>H<sub>4</sub>CHO, 104-87-0; *p*-MeOC<sub>6</sub>H<sub>4</sub>CHO, 123-11-5; CH<sub>3</sub>CH<sub>2</sub>CHO, 123-38-6; CH<sub>3</sub>CH(C-H<sub>3</sub>)CHO, 78-84-2; CH<sub>3</sub>C(CH<sub>3</sub>)<sub>2</sub>CHO, 630-19-3; MeCOPh, 98-86-2; Me<sub>2</sub>CO, 67-64-1; CH<sub>3</sub>CH<sub>2</sub>COCH<sub>2</sub>CH<sub>3</sub>, 96-22-0; cyclobutanone, 1191-95-3; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; cyclooctanone, 502-49-8; 2-(1-hydroxycyclohexyl)-2-phenylacetic acid, 5449-68-3.

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## Notes

### Preparation of 1-(Phenylthio)cyclopentenes and 1-(Phenylthio)cyclohexenes by the Pummerer Reaction

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The synthetic potential of vinyl sulfides, relatively stable enol derivatives, is already apparent. Grignard reagents under nickel(II) catalysis lead to stereoselective substitution or reduction<sup>1b,c,2</sup> of the vinyl carbon-sulfur bond while

palladium-catalyzed substitution of vinyl sulfides gives either 1-aryl or 2-aryl systems.<sup>3</sup> The Vilsmeier reaction produces  $\beta$ -sulfenylated  $\alpha,\beta$ -unsaturated aldehydes.<sup>4</sup> Lead tetraacetate or *N*-bromosuccinimide oxidize the allylic position, with the resulting acetate or bromide serving as an enolonium ion equivalent or as a precursor for sulfenylated enones.<sup>5</sup> Finally, reductive metalation can replace the vinyl carbon-sulfur bond with a metal ion,<sup>6</sup> while ox-

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