stirred autoclaves. Higher pressure experiments were run in the equipment described below.

High-Pressure Reactor and Compression System. All operations at high pressures were conducted in a steel-reinforced-concrete cell equipped with remote controls. Reactions were performed in a magnetically stirred 300-mL Autoclave-Engineers special heavy-duty autoclave rated for 3400 atm at 343 °C. The autoclave was heated by a large electric heating mantle. Cooling could be accomplished by passing a fluid through a groove between the inner lining and outer wall of the autoclave. Reaction temperatures were sensed by thermocouples that extended into a thermowell. Pressures in the system were measured by strain-gage pressure transducers.

A simplified diagram of the compression system appears in Figure 7. Rupture disk assemblies, most valves, and other accessories are not shown. A small compressor was used to feed the synthesis gas into two piston-driven compression cylinders and the autoclave. Typical pressures at this stage were 272–408 atm. The gas in the first cylinder was then forced into the second cylinder and the autoclave by advancing the piston with hydraulic fluid. The piston was advanced until the desired pressure was reached or until the piston had traveled the full length of the cylinder. When necessary, this procedure was repeated with the second compression cylinder.

Reactions. In each experiment, the autoclave was charged with catalyst components, promoters (if any), and 75.0 g of tetraglyme. The autoclave was closed and flushed with synthesis gas, and synthesis gas was added until the pressure was about 60% of the desired reaction pressure. Heating was then begun. Because of the very large mass of the autoclave, heatup required about 4 h. As the reaction temperature was reached, additional synthesis gas was added until the desired reaction pressure was reached. This point was considered as time zero. A proportional controller maintained the solution temperature within ±5 °C of the set point. During constant-pressure experiments, each time the pressure fell 13.6 atm below the desired pressure, it was increased by 27.2 atm by adding more synthesis gas. At a specified time, heating and stirring were stopped, and cooling fluid was passed through the autoclave. When the autoclave had cooled, unreacted synthesis gas was cautiously vented, and the product solution was recovered.

Products were analyzed by GLC on a Perkin-Elmer 3920B chromatograph using a thermal conductivity detector. Separations were achieved with a 6 ft × 0.25-in. column packed with 60/80 Chromosorb 101 that was held at 50 °C for 2 min, programmed at 16 °C/min to 260 °C, and maintained at 260 °C for 30 min. Product identities were determined by GLC/mass spectral analysis and were confirmed by retention time comparisons with authentic samples. Product yields were measured by comparing GLC peak areas to that of an added internal standard and were corrected for differences in detector responses. The ethylene glycol yield obtained by distillation of a product mixture was in very good agreement with that determined by GLC. The experimental results upon which Figures 2–4 and 6 are based are listed in Table IV.

Reactor Cleaning. During reactions, many of the metals (especially rhodium) deposited onto the walls, stirring impeller, stirring shaft, and thermowell of the autoclave. These deposits significantly influenced ensuing experiments. This problem was eliminated only by vigorous reaming of the autoclave body with steel wool spun by an electric drill and by using a small motor-powered brush to scour the other parts. This was done routinely after each experiment.

Acknowledgment. I am grateful to Dr. D. J. Strope and K. E. Cantrel for assembling the high-pressure experimental equipment and to I. L. Deal for experimental assistance.

Kinetics and Mechanism of the Conjugate Addition of Lithium Dimethylcuprate to α,β-Unsaturated Ketones

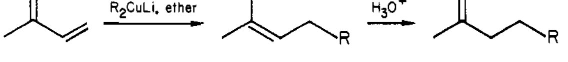
Susan Ruth Krauss and Stanley G. Smith*

Contribution from the Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801. *Received March 31, 1980*

Abstract: The kinetics of the reaction of several α,β-unsaturated ketones with excess lithium dimethylcuprate in the presence and absence of lithium iodide was studied by stopped-flow ultraviolet spectroscopy in diethyl ether solution at 25.0 °C, by measuring the rate of disappearence of a spectroscopically observable intermediate. Under these conditions, the conjugate additions are first order in ketone but exhibit a more complex dependence upon cuprate concentration. The rates of reaction of aryl-substituted 1-phenyl-3-methyl-2-buten-1-ones and β-aryl-substituted chalcones with $(CH_3)_2CuLi$ were also measured, and the rate and equilibrium constants for these reactions were correlated separately with Hammett σ constants. The rates of reaction of mesityl oxide and isophorone were also studied by stopped-flow infrared spectroscopy. Rapid scanning experiments in which reacting solutions of several enones were scanned over the carbonyl double-bond region of the infrared spectrum revealed the presence of an intermediate. These results are consistent with a mechanism in which the reactants are in equilibrium with an intermediate complex, which may unimolecularly rearrange to form a trialkylcopper(III) species with copper bonded to the β-carbon of the lithium enolate, followed by a reductive elimination process involving the copper ligands to form the β-methyllithium enolate product and methylcopper.

Introduction

Although the conjugate addition of lithium diorganocuprates to α,β-unsaturated ketones (eq 1) is widely used in organic synthesis,[1,2] the formulation of a detailed mechanism for this reaction has been impeded by the lack of kinetic data and by the scarcity of information regarding the structure and composition of these reagents in solution. Lithium dimethylcuprate has not been isolated,[2a] but two lithium diarylcuprates with intramolecular amine ligands were isolated and shown to exist in diethyl ether solutions as dimers, with each aryl group bridging a lithium and a copper atom.[3] Variable-temperature ^{13}C NMR studies of ethereal solutions of halide-free lithium dimethylcuprate showed only a single line for the methyl signals down to −80 °C,[4] and both proton[5–7] and carbon[6] NMR experiments on several cuprate



(1)

---

[1] (a) Gilman, H; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630. (b) House, H. O.; Respess, W. L.; Whitesides, G. M. *Ibid.* **1966**, *31*, 3128.

[2] For reviews, see: (a) Posner, G. H. *Org. React.* **1972**, *19*, 1; (b) House, H. O. *Proc. Robert A. Welch Found. Conf. Chem. Res.* **1974**, *17*, 101; (c) Singleto, E. *J. Organomet. Chem. C* **1975**, *R95*, 337; (d) Slocum, D. W. *Ibid.* **1975**, *R95*, 1.

[3] van Koten, G.; Noltes, J. G. *J. Chem. Soc., Chem. Commun.* **1972**, 940.

[4] House, H. O.; Chu, C.-Y. *J. Org. Chem.* **1976**, 3083.

[5] Pearson, R. G.; Gregory, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 4098.

[6] Kieft, R. L.; Brown, T. L. *J. Organomet. Chem.* **1974**, *77*, 289.

0002-7863/81/1503-141$01.00/0

reagents also indicated that the alkyl groups are magnetically equivalent.

^{1}H and ^{13}C NMR spectroscopic studies of diethyl ether solutions of lithium dimethylcuprate and methyllithium in various ratios failed to detect signals attributable to the formation of a third species,[8] but, by analogy to similar studies in other solvents and from indirect evidence, Ashby has proposed that $(CH_3)_5Cu_3Li_2$ and $(CH_3)_3CuLi_2$ also can exist in diethyl ether solution, depending upon the $(CH_3)_2CuLi$:CH_3Li ratio.[8-10] The molecular weight of lithium dimethylcuprate determined from vapor-pressure depression measurements[5] and from ebullioscopic measurements[8] indicated that this compound exists as a dimer in diethyl ether solution. Solution X-ray scattering studies[5] were interpreted in terms of a cyclic dimeric structure for the cuprate cluster, although this interpretation has been questioned.[7,11]

Lithium dimethylcuprate reacts with alkyl halides and tosylates to form the coupled product (eq 2).[12] The results of stereo-

$$RX + [(CH_3)_2CuLi]_2 \xrightarrow{\text{ether}} R\text{-}CH_3 + (CH_3)_3Cu_2Li_2^+ + X^- \quad (2)$$

chemical studies indicate that the reaction proceeds with predominant inversion of configuration at the carbon bearing the leaving group.[13,14] The reactions of $(CH_3)_2CuLi$ with *n*-octyl tosylate[14] and methyl iodide[5] in ether were found to adhere to a second-order rate law. These data are consistent with a mechanism involving oxidative addition at copper of the substrate, leading to a trialkylcopper(III) species, followed by reductive elimination to yield the coupled product.[15] An alternative mechanism involving the intermediacy of $(CH_3)_5Cu_2{}^{II}Li_2{}^+$ has also been suggested.[5] A trialkylcopper(III) species also has been proposed as an intermediate in the reaction of lithium dialkycuprates with oxiranes,[16] propargylic acetates and halides,[17] and vinylic halides,[18] as well as in the reaction of copper enolates of esters with propargylic substrates[19] and the reaction of CH_3MgCl/CuI with 1-phenylpropargyl tosylate.[20]

House[21] has suggested that the conjugate addition of $(CH_3)_2CuLi$ to an enone proceeds by an initial coordination of the carbonyl oxygen atom to the cuprate cluster, followed by electron transfer from the cuprate to the ketone to form an anion radical and an electron-deficient metal cluster. Rebonding of these two species at the sites of high-spin density, followed by intramolecular transfer of a methyl group from the metal cluster to the β-carbon of the enone, leads to the products. It has been proposed that the equilibrium position for the reversible transfer of an electron can be estimated from the electrode potentials for oxidation of the cuprate and reduction of the enone.[22] House presented a qualitative correlation between the reduction potentials of α,β-unsaturated carbonyl compounds and their ability to undergo conjugate addition with $(CH_3)_2CuLi$.[23] The redox characteristics of the cuprate further suggest that a necessary first step in the conjugate addition reaction is coordination of the carbonyl oxygen to the cuprate metal cluster.[4,22] ^{13}C NMR, Raman, and visible spectral measurements indicate that the site of complexation at the cuprate cluster is at a lithium atom, rather than at copper.[4]

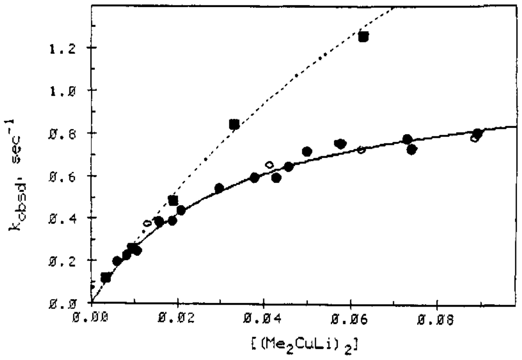
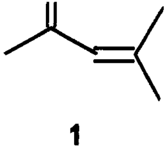


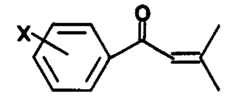
Figure 1. Plot of k_{obsd} vs. concentration of dimeric lithium dimethylcuprate for the reaction of mesityl oxide in diethyl ether at 25.0 °C. The solid curve was calculated from eq 5 with K = 30 M^{-1} and k = 1.12 s^{-1} and was based on data obtained from solutions of reagent containing approximately three equivalents of lithium iodide. The points denoted by a solid circle were measured at 340 nm and those designated by an open circle were measured at 380 nm. The dashed curve was obtained from eq 5 with K = 7.9 M^{-1} and k = 3.9 s^{-1} and was based on data obtained from measuring the rate of reaction at 380 nm of halide-free reagent solutions (■).

Although the alkylative ring opening of β-cyclopropyl-α,β-unsaturated ketones which accompanies the conjugate addition of $(CH_3)_2CuLi$ has been cited as evidence for the formation of an intermediate anion radical,[24] recent work by Casey and Cesa[25] has shown that the ring opening is highly stereospecific, providing evidence against an anion radical intermediate and in favor of a direct nucleophilic attack of the cuprate on the cyclopropyl ring. Additional evidence supporting the electron-transfer mechanism comes from the cis–trans isomerization which was observed to occur concurrently with the conjugate addition of lithium dimethylcuprate.[26] No ESR[11] or CIDNP[27] signals directly attributable to intermediate radical anions formed during the course of conjugate addition have been observed, although there is some evidence that $(CH_3)_2CuLi$ can transfer an electron to benzophenone to form a radical anion.[4,28]

While no measurements of the absolute rates of reaction of lithium dimethylcuprate with unsaturated ketones have been reported, House has performed some competitive kinetics experiments.[4] The results of the competition of enones **1** and **2a** for a deficiency of cuprate were interpreted to indicate that reaction of the more easily reduced enone **2** with $(CH_3)_2CuLi$ is slightly more rapid than the corresponding reaction of **1**.[29]



1



2a, X = H
b, X = p-OC$_6$H$_5$
c, X = p-CH$_3$
d, X = p-Cl
e, X = m-CF$_3$

---

(7) Filippo, J. S., Jr. *Inorg. Chem.* **1978**, *17*, 275.

(8) Ashby, E. C.; Watkins, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 5312.

(9) Ashby, E. C.; Watkins, J. J. *J. Chem. Soc., Chem. Commun.* **1976**, 784.

(10) (a) Still, W. C.; Macdonald, T. L. *Tetrahedron Lett.* **1976**, 2659. (b) Ashby, E. C.; Lin, J. J.; Watkins, J. J. *Ibid.* **1977**, 1709. (c) Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280. (d) Ashby, E. C.; Lin, J. J. *J. Org. Chem.* **1977**, *42*, 2805.

(11) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893.

(12) Posner, G. H. *Org. React. (N.Y.)* **1975**, *22*, 253.

(13) Whitesides, G. M.; Fischer, W. F.; Filippo, J. S., Jr.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.

(14) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783.

(15) Posner, G. H.; Ting, J.-S. *Tetrahedron Lett.* **1974**, 683.

(16) (a) Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1977**, *42*, 2537. (b) Johnson, C. R.; Her, R. W.; Wieland, D. M. *Ibid.* **1973**, *38*, 4263. (c) Herr, R. W.; Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 3813.

(17) (a) Luche, J. L.; Barreiro, E.; Dollat, J.-M.; Crabbé, P. *Tetrahedron Lett.* **1975**, 4615. (b) Crabbé, P.; Barreiro, E.; Dollat, J.-M.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1976**, 183. (c) Dollat, J.-M.; Luche, J.-L.; Crabbé, P. *Ibid.* **1977**, 761.

(18) (a) Klein, J.; Levene, R. *Tetrahedron Lett.* **1974**, 2935. (b) Klein, J.; Levene, R. *J. Am. Chem. Soc.* **1972**, *94*, 2520.

(19) Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 555.

(20) Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 112.

(21) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443.

(22) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

(23) House, H. O.; Umen, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 5495.

(24) (a) Marshall, J. A.; Ruden, R. A. *Tetrahedron Lett.* **1971**, 2875. (b) Marshall, J. A.; Ruden, R. A. *J. Org. Chem.* **1972**, *37*, 659. (c) House, H. O.; Snoble, K. A. J. *Ibid.* **1976**, *41*, 3076.

(25) Casey, C. P.; Cesa, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4236.

(26) House, H. O.; Weeks, P. D. *J. Am. Chem. Soc.* **1975**, *97*, 2770.

(27) Hannah, D. J.; Smith, R. A. J. *Tetrahedron Lett.* **1975**, 187.

(28) Smith, R. A. J.; Hannah, D. J. *Tetrahedron* **1979**, *35*, 1183.

(29) House, H. O.; Prabhu, A. V.; Wilkins, J. M.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 3067.

The purpose of the present study was to obtain additional understanding of the mechanism of reaction of lithium dimethylcuprate with α,β-unsaturated ketones, by determining the rate law of the reaction and by measuring the effects of ketone structure and reagent composition upon the absolute rates of reaction.

Results

Kinetics of Conjugate Addition of Lithium Dimethylcuprate–Lithium Iodide to α,β-Unsaturated Ketones. The rate of reaction of mesityl oxide (**1**) with lithium dimethylcuprate was studied by stopped-flow ultraviolet spectroscopy at 25.0 °C in diethyl ether solution (containing approximately 3 equiv of lithium iodide) at ketone concentrations of $(1.4–8.9) \times 10^{-3}$ M and dimeric reagent concentrations of $(0.61–8.9) \times 10^{-2}$ M. The rate of reaction was measured by following the disappearance of a spectroscopically observable intermediate which was formed in less than 1 ms, the time elapsed between mixing and the initial spectroscopic observation. In all cases excellent adherence to a first-order rate law was observed, with standard plots linear over at least 95% of the reaction. The observed pseudo-first-order rate constants, k_{obsd}, are obtained from unweighted linear least-squares analyses of the first-order plots. The measured rate constants were approximately independent of initial ketone concentration.

The dependence of the observed pseudo-first-order rate constant upon the concentration of dimeric lithium dimethylcuprate, as shown in Figure 1, is nonlinear. These data can be described accurately by the rate law in eq 3, in which the cuprate has been

$$-\frac{d[\text{intermediate}]}{dt} = \frac{kK[(CH_3)_4Cu_2Li_2][\text{ketone}]}{1 + K[(CH_3)_4Cu_2Li_2]} \quad (3)$$

represented as a dimer. Equation 3 mathematically describes the mechanistic scheme depicted in eq 4. The expression for the

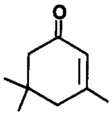
$$\text{ketone} + (CH_3)_4Cu_2Li_2 \overset{K}{\rightleftharpoons} \text{intermediate} \xrightarrow{k} \text{products} \quad (4)$$

pseudo-first-order rate constant is depicted in eq 5. The values

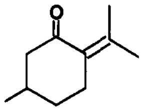
$$k_{obsd} = \frac{kK[(CH_3)_4Cu_2Li_2]}{1 + K[(CH_3)_4Cu_2Li_2]} \quad (5)$$

of the equilibrium constant, K, and the rate constants, k, were extracted from an unweighted least squares analysis of a plot of k_{obsd}^{-1} vs. $[(CH_3)_4Cu_2Li_2]^{-1}$ and then adjusted with the aid of a computer to obtain the apparent best fit to the data. The adjustment was necessary because the double reciprocal plot shows the most sensitivity to the points at low concentrations while the direct plot exhibits the most sensitivity to the points at high cuprate concentrations.

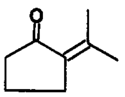
The reactions of lithium dimethylcuprate with a series of other ketones, isophorone (**3**), (+)-pulegone (**4**), 2-isopropylidenecyclopentanone (**5**), 2,5-diisopropylidenecyclopentanone (**6**), and dypnone (**7**), were studied. These reactions were all performed in diethyl ether at 25.0 °C, and the rates of the reactions were again measured by monitoring the disappearance of a spectroscopically (ultraviolet) observable intermediate. These reactions could all be described by the same rate law, eq 3, and the rate and equilibrium constants for these reactions are summarized in Table I.



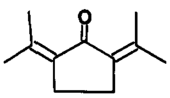
3



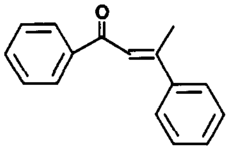
4



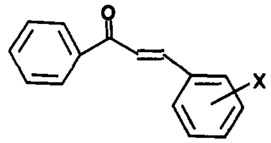
5



6



7



8a, X = H

b X = p-OCH$_3$

c, X = p-CH$_3$

d, X = p-Cl

e, X = m-CF$_3$

Table I. Summary of Rate and Equilibrium Constants for the Reaction of Lithium Dimethylcuprate–Lithium Iodide with Selected Enones in Diethyl Ether at 25.0 °C

ketone	K, M^{-1}	k, s^{-1}
1	30 (7.9^a)	1.12 (3.9^a)
3	110	0.089
4	40	0.062
5	36 (7.0^a)	0.17 (0.99^a)
6	11	0.21
7	20	1.45

^{a} Halide-free reagent.

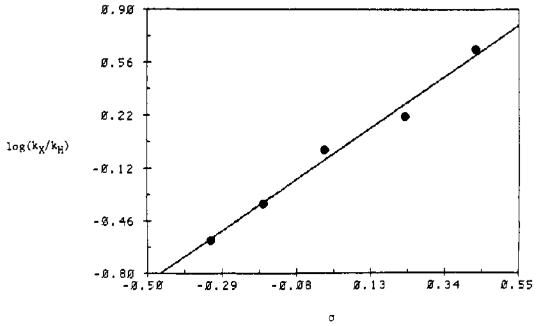


Figure 2. Correlation of the relative rate constants for the conjugate addition of lithium dimethylcuprate–lithium iodide to substituted 1-phenyl-3-methyl-2-buten-1-ones in diethyl ether at 25.0 °C with σ constants.

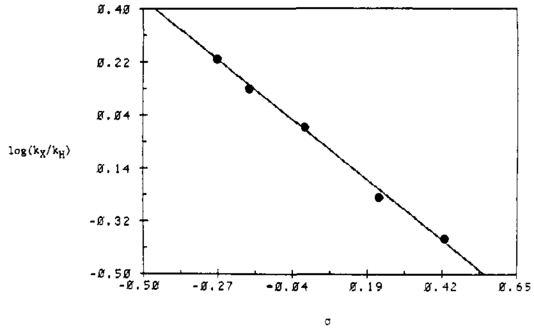


Figure 3. Correlation of the relative rate constants for the conjugate addition of lithium dimethylcuprate–lithium iodide to substituted chalcones in diethyl ether at 25.0 °C with σ constants.

Rapid-scanning experiments, in which the spectrum of the reacting solution in the UV stopped-flow instrument was repeatedly recorded, revealed in the case of ketones **1**, **3**, and **4** that the λ_{max} of the intermediate is obscured by the absorbance of the cuprate. The reactions were all followed on shoulders of the absorbances due to the respective intermediates. The reaction of mesityl oxide was studied at 340 and 380 nm, and the observed rate constants were independent of wavelength. The reactions of the other ketones were all studied at 380 nm. At this wavelength the ketones were all transparent at the concentrations used in these experiments.

Substituent Effects on Rate of Conjugate Addition to Unsaturated Aryl Ketones. The rates of reaction of aryl-substituted 1-phenyl-3-methyl-2-buten-1-ones (**2a–e**) and β-aryl-substituted chalcones (**8a–e**) with lithium dimethylcuprate–lithium iodide were also measured, and the rate and equilibrium constants for these reactions were correlated separately with Hammett σ constants. A plot of log (k_X/k_H) vs. σ has a slope (ρ) of +1.58 for the reaction of substituted 1-phenyl-3-methyl-2-buten-1-ones (Figure 2) and a ρ value of −0.88 for the reaction of substituted chalcones (Figure 3). Both plots of log (K_X/K_H) vs. σ were curved; for the chalcone series the plot exhibited a maximum for the unsubstituted substrate (Figure 4) and for the 1-phenyl-3-methyl-2-buten-1-one series

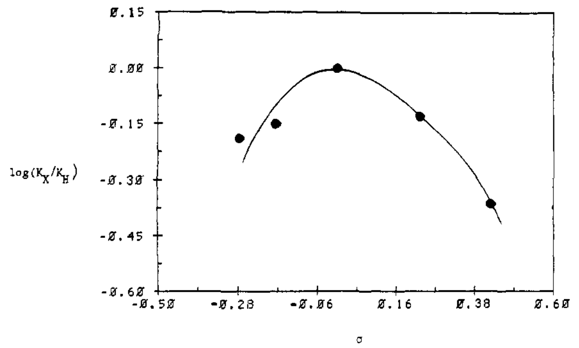


Figure 4. Correlation of the relative equilibrium constants for the conjugate addition of lithium dimethylcuprate–lithium iodide to substituted chalcones in diethyl ether at 25.0 °C with σ constants.

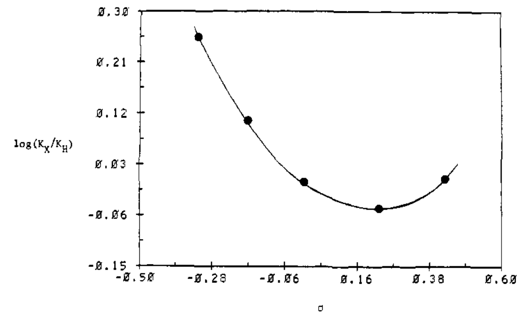


Figure 5. Correlation of the relative equilibrium constants for the conjugate addition of lithium dimethylcuprate–lithium iodide to substituted 1-phenyl-3-methyl-2-buten-1-ones in diethyl ether at 25.0 °C with σ constants.

exhibited a minimum for the 4-chloro-substituted compound (Figure 5).

Reaction of Lithium Dimethylcuprate with 2,2,6,6-Tetramethylcyclohexanone. A 0.023 M solution of 2,2,6,6-tetramethylcyclohexanone in 0.60 M lithium dimethylcuprate–lithium iodide had an absorbance of 0.038 at 380 nm while the reagent had an absorbance of 0.015. This saturated ketone was recovered unreacted from the reaction mixture after ca. 5 min. Since the ketone alone does not absorb at this wavelength, the change in absorbance must be due to some type of interaction between the reagent and the ketone.

Conjugate Addition of Halide-Free Lithium Dimethylcuprate to Enones. The rates of reaction of halide-free lithium dimethylcuprate with mesityl oxide and 2-isopropylidenecyclopentanone were measured by following the disappearance of an intermediate (monitored at 380 nm) which was present as soon as the reacting solution reached the cell. The reactions of this halide-free reagent all followed the same general rate law (eq 3). As seen in Figure 1 and Table I, under the conditions used in these experiments, the reactivity of the cuprate is higher when the lithium iodide is not present in the solutions.

Studies in the Infrared. The rate of reaction of isophorone with lithium dimethylcuprate–lithium iodide was studied by infrared stopped-flow spectroscopy at 25.0 °C in diethyl ether solution at a ketone concentration of 0.013 M and dimeric reagent concentrations of 0.028–0.085 M. The rates were measured by monitoring the disappearance of the 1675–1680-cm^{-1} carbonyl band of the ketone. The kinetic data gave linear second-order rate plots. The dependence of the calculated pseudo-first-order rate constants upon the concentration of the dimeric cuprate is illustrated in Figure 6 as well as the data obtained from presumably the same reaction followed in the ultraviolet.

Experiments in which a reacting solution of mesityl oxide (**1**), 1-(4-methylphenyl)-3-methyl-2-buten-1-one (**2c**), or isophorone (**3**) and lithium dimethylcuprate were scanned over the carbonyl double-bond region (ca. 5.8–6.6 μm) of the infrared spectrum revealed the presence of an intermediate. The bands due to the carbonyl and carbon–carbon double bonds in the spectrum of the reacting solution were noticeably broadened relative to those in the spectrum of the initial ketone solution. The spectra of these intermediates could be reproduced by mixing the respective ketones with a solution of lithium iodide in diethyl ether.

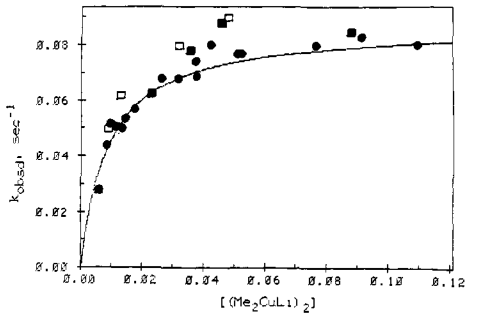


Figure 6. Plot of k_{obsd} vs. concentration of dimeric lithium dimethylcuprate for the reaction of isophorone in diethyl ether containing approximately 3 equiv of lithium iodide. The points designated by a solid circle were measured at 380 nm, those denoted by a open box were measured at 1676 cm^{-1}, and those indicated by a solid box were obtained at 1680 cm^{-1}. The curve was based on the data measured at 380 nm and was obtained from eq 5 with $K = 110$ M^{-1} and $k = 0.089$ s^{-1}.

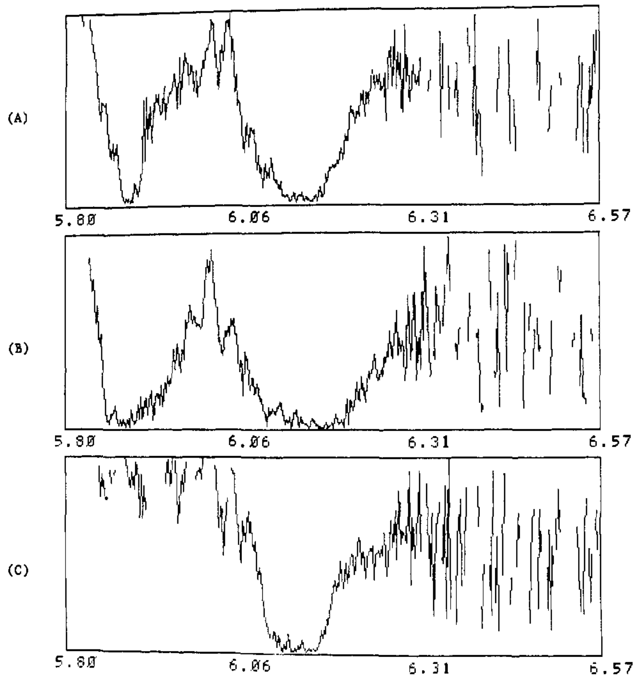


Figure 7. Spectra obtained at 25.0 °C in diethyl ehter. (A) Plot of percent transmission vs. wavelength for 2.6 × 10^{-2} M mesityl oxide. (B) Plot of percent transmission vs. wavelength for a reacting mixture of 2.9 × 10^{-2} M (dimeric) halide-free lithium dimethylcuprate and 2.6 × 10^{-2} M mesityl oxide. (C) Plot of percent transmission vs. wavelength for the cuprate enolate formed from the conjugate addition of 2.9 × 10^{-2} (dimeric) halide-free lithium dimethylcuprate to 2.6 × 10^{-2} M mesityl oxide. The spectra are digitized by using 384 data points and generated by subtracting the absorbance spectrum of the solvent, diethyl ether, from the absorbance spectrum of interest. These spectra were all recorded at 25.0 °C and are each the average of 4 scans.

Reacting solutions of halide-free lithium dimethylcuprate, either mesityl oxide (**1**) or isophorone (**3**), and 2-isopropylidenecyclopentanone (**5**) were also scanned over the carbonyl double-bond region, and similar spectral changes were observed. In the case of 2-isopropylidenecyclopentanone (**5**) the spectrum of the intermediate was also reproduced by mixing the ketone solution with a lithium iodide solution.

Figure 7, which illustrates the spectra of mesityl oxide, a reacting solution of mesityl oxide and halide-free lithium dimethylcuprate, and the enolate product of the reaction prior to hydrolysis, is representative of the changes which occur in the infrared spectrum over the course of the reaction. The position and shape of the enolate carbon–carbon double-bond absorption

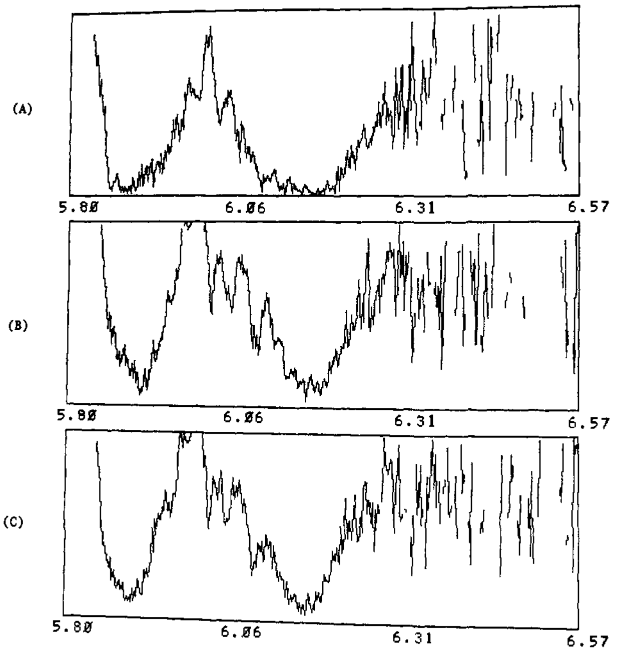


Figure 8. (A) Plot of percent transmission vs. wavelength for a reacting mixture of 2.9×10^{-2} M (dimeric) halide-free lithium dimethylcuprate and 2.6×10^{-2} M mesityl oxide. (B) Plot of present transmission vs. wavelength for a reacting mixture of 4.2×10^{-2} M (dimeric) lithium dimethylcuprate–lithium iodide and 1.4×10^{-2} M mesityl oxide. (C) Plot of present transmission vs. wavelength for 1.4×10^{-2} M mesityl oxide in 0.19 M lithium iodide. The spectra are digitized by using 384 data points and generated by subtracting the absorbance spectrum of the solvent, diethyl ether, from the absorbance spectrum of interest. These spectra were all recorded at 25.0 °C and are each the average of 4 scans.

are the same as that of the enone.

Figure 8 shows the spectra of a reacting solution of halide-free lithium dimethylcuprate and mesityl oxide, a reacting solution of halide-containing lithium dimethylcuprate and this ketone, and a solution of mesityl oxide and lithium iodide. These three spectra are very similar, suggesting that the type of complex formed between the enone and lithium iodide can serve as a model for the intermediate which is observed. Whether the changes observed in the spectrum of a reacting solution of an enone and the halide-containing cuprate, relative to that of the enone, are caused by complexation of the enone by the reagent, by lithium iodide, or by both species has not been determined.

Discussion

Reagent Structure. Any proposed mechanism for the conjugate addition of $(CH_3)_2CuLi$ to α,β-unsaturated ketones is premised on an assumed structure for the reagent. It has been shown that halide-free $(CH_3)_2CuLi$ exists as a dimer in diethyl ether,[5,8] although the arrangement of metal atoms is uncertain.[5,7,11] Little is known about the structure of the cuprate in the presence of lithium iodide; it is possible that the iodide is incorporated into the cuprate cluster. In the absence of definitive information to the contrary, the structure of $(CH_3)_2CuLi$ in the presence of lithium iodide will be represented throughout this report as the cyclic dimeric structure depicted by House.[21]

General Spectroscopic Observations. The α,β-unsaturated ketones studied do not absorb at 380 nm at the concentrations used for the rate measurements. However, in the presence of lithium iodide the λ_{max} of the $\pi-\pi^*$ absorption is shifted to longer wavelengths, and the lithium iodide–enone complex does absorb at 380 nm. For example, an ethereal solution of 5×10^{-3} M mesityl oxide (**1**), which was also 0.11 M in lithium iodide had an absorbance of 0.11 at 380 nm, and a 6×10^{-4} M solution of chalcone (**8a**), which was also 0.11 M in lithium iodide, had an absorbance of 0.41 at 380 nm. For these two representative substrates, complexation of the enone with lithium iodide will certainly contribute to the changes observed in the ultraviolet spectrum. The reactions of halide-free $(CH_3)_2CuLi$ with several enones were also studied by measuring the rate of disappearance of a spectroscopically observable intermediate at 380 nm. Thus, lithium iodide is not necessary for the formation of an intermediate species with a strong absorbance at this wavelength.

Scanning the infrared spectra of reacting solutions of both halide-free and halide-containing $(CH_3)_2CuLi$ revealed an intermediate in which the carbon–carbon double bond and carbonyl bands were noticeably broadened (parts A and B of Figure 8, respectively). Since the spectrum of the intermediate was quite similar in both cases, lithium iodide is neither necessary nor solely responsible for the spectral changes observed. This intermediate spectrum could be approximated by adding lithium iodide to the ketone solution (Figure 8C). Thus, complexation between lithium iodide and the carbonyl oxygen can serve as a model for the type of interaction between the cuprate and the enone which gives rise to the observed spectral changes.

With the halide-containing solutions it is possible that the cuprate competes with the lithium iodide for a complexation site at the carbonyl oxygen. House and co-workers have shown that the ^{13}C NMR signals due to the carbonyl carbon and β-carbon of several enones are shifted downfield in the presence of $LiClO_4$ but not in the presence of various copper(I) or copper(II) salts.[4] The observation that donor solvents accelerate the coupling reaction of cuprates with alkyl halides but slow down the presumably mechanistically similar conjugate addition to enones was also interpreted in terms of the cuprate complexing with the enone through the lithium ion.[23] On the basis of this literature evidence as well as the fact that lithium ion is more electropositive than copper, it will be assumed that the site of carbonyl group complexation on the cuprate cluster is at lithium.

Kinetics of Reaction of Enones with $(CH_3)_2CuLi$–LiI. The rates of reactions studied exhibited a first-order dependence on ketone concentration and a more complex dependence upon cuprate concentration. The observed kinetic behavior is consistent with a rate law (eq 3) derived from a mechanistic scheme (eq 4) in which the reactants are in equilibrium with an intermediate species, which then unimolecularly rearranges to form the observed products. With the available data, this scheme is indistinguishable from one in which the intermediate is not on the reaction pathway. The plots of k_{obsd} vs. dimeric cuprate concentration are quite sensitive to the value of the rate constant but not particularly sensitive to the value of the equilibrium constant; hence, the derived values of the equilibrium constant, K, are subject to greater uncertainty than are the rate constants, k.

Table I summarizes the equilibrium and rate constants for the reactions of six α,β-unsaturated ketones. Mesityl oxide (**1**), isophorone (**3**), and (+)-pulegone (**4**) each possess a different conformational arrangement about the enone skeleton. In pulegone (**4**) the carbon–carbon double bond is locked in a cisoid conformation with respect to the carbonyl group, in isophorone it is locked in a transoid conformation, and in mesityl oxide it has free mobility to attain the most favorable conformation. Each of these ketones possesses a similar steric environment about the β-carbon atom. The relative values of the equilibrium constants seem to reflect the steric bulk about the carbonyl. Isophorone (**3**) has the least sterically hindered carbonyl and also the largest equilibrium constant. 2,5-Diisopropylidenecyclopentanone (**6**) has the smallest equilibrium constant, and it has the most sterically hindered carbonyl group. Pulegone (**4**) and 2-isopropylidenecyclopentanone (**5**) possess carbonyl groups with approximately the same steric environment, and their equilibrium constants are quite similar.

A cisoid conformation about the enone skeleton is clearly not essential since isophorone (**3**) has the largest apparent equilibrium constant. The above discussion of the relative values of the equilibrium constants assumes that the cuprate is complexing only through lithium to the carbonyl oxygen of the enone. Alternatively, the cuprate may be coordinated through lithium to the oxygen and through copper to the β-carbon.

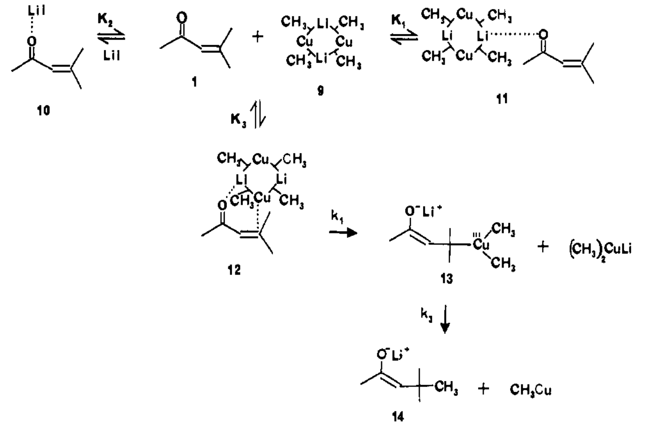
If the species in equilibrium with the reactants involves a complex at the carbonyl oxygen, as suggested by the infrared data, then for all the ketones studied except **6** there exist two sites of

Table II. Comparison of Reduction Potentials with Rate and Equilibrium Constants for Representative Enones

ketone	E_{red}[a]	K, M^{-1}	k, s^{-1}	ref
8a	−1.41	162	5.0	33
2a	−1.86	8.6	13.8	29
1	−2.21	30	1.12	29
3	−2.22[b]	110	0.089	33

[a] E_{red} values in V vs. SCE measured in aprotic solvent. [b] This value was obtained from 3,5-dimethyl-2-cyclohexenone.

Scheme I



complexation, one syn to the double bond and one anti. The kinetic data obtained from the reaction of 2,5-diisopropylidenecyclopentanone adhered to the same rate law as did the other, nonsymmetric ketones, indicating that if these latter ketones do form a complex with the cuprate which is situated anti to the double bond, it is not the only complex formed. It is likely that the complex formed in the anti position would only revert to reactants.

The rate constant for the reaction of mesityl oxide is significantly larger than those for the other ketones. Mesityl oxide is the only ketone of the group which possesses a double bond which is not conformationally rigid, so this molecule can adopt the lowest energy conformation in the transition state. No trends can be discerned from the rate constants for the reactions of the four other ketones, since their values are all quite similar. There is little difference between the rate constant for isophorone, in which the double bond is locked in a transoid position, and that for pulegone, in which the double bond is locked in a cisoid conformation.

Table II summarizes the reduction potentials and rate and equilibrium constants for four representative enones. If this reaction were proceeding through a rate-limiting electron-transfer step, it is reasonable to expect a correlation between the reduction potential of the substrate and its rate of reaction. However, neither the rate nor equilibrium constants change monotonically as the reduction potential of the substrate decreases.

Proposed Mechanism for the Conjugate Addition of Halide-Containing Lithium Dimethylcuprate to α,β-Unsaturated Ketones. A reaction pathway[14] which appears to be consistent with the kinetic and spectroscopic data collected in this study is depicted in Scheme I for the reaction of mesityl oxide. The reactants are in equilibrium with three species of which only one, **12**, is on the reaction pathway leading to the 1,4 adduct. A pathway for formation of the conjugate addition product could involve formation of intermediate complex **12** in which the cuprate is complexed to the β-carbon through copper with possible additional interaction between lithium and the carbonyl oxygen where geometry permits. Complex **12** could then intramolecularly rearrange to form a trialkylcopper(III) species, **13**, with concurrent loss of an equivalent of $(CH_3)_2CuLi$. Complex **13** then intramolecularly rearranges with transfer of a methyl group to the beta carbon to form **14** and methylcopper, a reductive elimination process involving the copper ligands.

The equilibrium constant, K, obtained from the treatment of the kinetic data (eq 3), would be a composite of the equilibrium constants for formation of complexes **10**–**12**. The values of the equilibrium constants reflect both steric and electronic effects at the carbonyl group.

Lithium ion is known to complex with the oxygen atom of a carbonyl functionality in ether solvents.[31,32] Under the present reaction conditions, it is reasonable to assume that any free lithium iodide will interact with the enone to form complex **10**. When lithium iodide was added to an ethereal solution of an enone, the infrared spectral changes observed were quite similar to those observed in the reacting solution of $(CH_3)_2CuLi$, suggesting that a lithium iodide–enone complex could be partially responsible for the changes observed in the infrared spectrum of a reacting solution (Figure 7). Additional support for formation of this complex comes from a comparison of the equilibrium constants for the reaction of ketones **1** and **5** with halide-containing and halide-free reagents. The former reagent has larger values, consistent with the presence of this additional equilibrium.

The curved Hammett plots obtained from the study of dependence of the equilibrium constant, K, upon substituents in the α and β aromatic rings of 1-phenyl-3-methyl-2-buten-1-one (**2**) and chalcone (**8**), respectively, are in agreement with a mechanism in which the reactants are in equilibrium with various species whose formations have different electronic demands. The electronic changes which accompany the transformation of **12** to **13** are consistent with the results obtained from the study of the dependence of the rate constant, k, upon the electron density in the α and β aromatic rings of **2** and **8**. The ρ value of +1.58 obtained from the former study is consistent with the development of negative charge at the carbonyl carbon. The ρ value of −0.88 obtained indicates the formation of positive charge at the β-carbon.

The transformation of **13** to **14**, which is written as lithium enolate as suggested by House,[21] involves very little electronic reorganization at the original carbonyl carbon. Therefore it is unlikely that the ρ values reflect this step in the reaction sequence. It appears that the results of the substituent studies are consistent with the slowest step being the conversion of **12** to **13**.

The reactants may also be in equilibrium with a charge-transfer complex which could account for the spectral changes observed in the ultraviolet region, as well as for the transient bright orange or red color observed when the cuprate is mixed with an enone. House and Chu[4] suggested that a charge-transfer complex was responsible for the red color observed when an ethereal solution of benzophenone was mixed with a solution of $(CH_3)_2CuLi$ at temperatures between −70 and 0 °C. It is also possible that the reactants are in equilibrium with a trace amount of an anion radical and an electron-deficient cuprate, which would account for the results of the stereochemical test derived by House and Weeks.[26]

The presence of lithium iodide in the cuprate solutions, in addition to complexing with the enone, probably alters the composition of the cuprate cluster. Although for the purpose of this discussion the cuprate has been conveniently represented as the cyclic dimer, **9**, depicted by House,[21] the iodide may be incorporated in the cuprate cluster.

Experimental Section

General Data. Ultraviolet spectra were recorded with a Perkin-Elmer Model 202 spectrophotometer using matched 1-cm quartz cells. Infrared spectra were obtained on a Perkin-Elmer Model 237B or Beckman Model IR-12 spectrophotometer. Nuclear magnetic resonance spectra were obtained on Varian T-60 or EM-390 spectrometers and are reported in parts per million downfield from internal Me_4Si. Analytical data were obtained by Mr. J. Nemeth and associates at the University of Illinois, and all compounds prepared gave satisfactory analyses for carbon, hydrogen, and halogen when present. Melting points were determined on a Büchi melting point apparatus in open capillaries and are uncorrected.

---

(30) Hammett, L. P. "Physical Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1970; p 26.

(31) Wong, M. K.; McKinney, W. J.; Popov, A. I. *J. Phys. Chem.* **1971**, *75*, 56.

(32) Wiegers, K. E.; Smith, S. G. *J. Org. Chem.* **1979**, *43*, 1126.

(33) House, H. O.; Huber, L. E.; Umen, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 8471.

Syringe transfers of lithium dimethylcuprate and methyllithium solutions were made by using calibrated Hamilton gas-tight syringes.

Gas chromatographic analyses were performed with a Hewlett-Packard F&M Scientific 700 laboratory chromatograph equipped with a thermal conductivity detector. Analyses were performed on an 8 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W (DMCS) column. Peak areas were measured by disk integration, and solutions containing an internal standard were corrected for thermal conductivity responses. The GC trace of each volatile ketone studied exhibited only a single peak.

Kinetic Measurements and Data Analysis. All ultraviolet kinetic experiments were performed on a stopped-flow spectrophotometer[34] with a rapid-scan capability,[35] which has been described previously. Infrared kinetic experiments were performed by using stopped-flow instrumentation,[36] which has also been described previously and modified as follows. A continuous radiation source is obtained from the infrared component of light from a zirconium oxide concentrated arc lamp.[37] This lamp, which has a magnesium fluoride lens, is enclosed in an argon-filled, water-cooled jacket. Rapid-scanning capability is provided by a synchronous stepping motor, with the appropriate electronics to choose from a variety of scanning speeds, which drives the monochromator. Both stopped-flow instruments were maintained at a temperature of 25.0 ± 0.1 °C by means of thermostated ethylene glycol baths.

Kinetic data were collected on a 32-channel analog input buffer, collecting points at intervals of 5 ms to 10 s. These data, together with the zero-light level and infinity reading (taken after at least ten half-lives), were then transferrred to disk storage on the PLATO IV computer-based education system CDC Cyber 73 computer.[38] Curves of percent transmittance vs. time were computer-generated by connecting the 32 digitized light level measurements with straight line segments. Kinetic data were treated either as pseudo-first-order in ketone or, when the reagent was not present in large excess, as second-order. The rate plots typically were linear over at least 5 half-lives. Rate constants taken from unweighted least-squares analysis of the transmittance data generally were reproducible to within ca. 5%. The code for the computer programs used for the data analysis has appeared elsewhere.[39]

Infrared spectra obtained under rapid-scanning conditions were generated by digitizing 384 transmittance measurements at a time interval of 0.01 s. The data were collected in an input buffer, transferred to an off-line PLATO V computer terminal,[40] and stored on a floppy disk. Each scan was repeated four times and the averaged spectrum reported. Such spectra were determined for the solvent, the ketone solution, the reacting solution, and the product solution, and spectral comparisons were effected by having the computer generate a spectrum of the sample by using the spectrum of the solvent as the base line.

Preparation of Solutions of $(CH_3)_2CuLi$. Solutions of lithium dimethylcuprate were prepared in an all-glass, grease-free apparatus which was dried and deoxygenated by repeatedly evacuating to less than 1 mm and filling with argon (Linde, passed through a column of BTS catalyst to remove oxygen and also through 4-Å molecular sieves). The apparatus was also flamed prior to use. Reagent grade diethyl ether (Mallinckrodt or Drake) was freshly distilled from methyllithium. Hexane (distilled in glass, Burdick & Jackson Laboratories) was used to transfer excess lithium sand,[41] prepared from Foote Mineral Company reactor grade lithium, into one of two parallel flasks which were connected by a calibrated holding vessel. The hexane was then pumped off, and an addition flask containing a solution of purified[42] iodomethane (Aldrich) in dry ether was attached to the flask and degassed. Ether was distilled onto the lithium sand, and the ethereal iodomethane was then added over a period of 2.5–3 h to the ice-cold, stirred slurry of lithium sand. The resulting methyllithium–lithium iodide solution was stirred at room temperature for a few hours and then allowed to settle for 20–40 h.

Immediately prior to preparing the cuprate solution, samples of the methyllithium solution were analyzed for total base and weak base titers by the Gilman method.[43] A 1.03-equiv sample of purified[44] cuprous iodide was then added to the flask parallel to the flask containing CH_3Li. After degassing the CuI and distilling ether onto it, the CH_3Li solution was filtered by argon pressure through sintered glass into the calibrated holding vessel, from which it was added over a period of 1–1.5 h to the ice-cold, stirred slurry of CuI. The resulting, frequently black, solution was stirred for several hours, during which time it was allowed to warm to room temperature. After the solution settled for 12–18 h, the clear, nearly colorless supernatant was filtered twice by argon pressure through sintered glass and delivered into silicone rubber serum capped bottles. In order to get a range of concentrations, we diluted some of the solutions by the addition of freshly distilled ether directly into the bottles. Ketone solutions were prepared by distillation of dry ether into bottles containing weighed amounts of degassed ketone.

Halide-free lithium dimethylcuprate was prepared from the reaction of halide-free CH_3Li (prepared from the reaction of $(CH_3)_2Hg$ with lithium sand[45]) with halide-free CH_3Cu by using the apparatus described above. The methylcopper, prepared from the reaction of purified CuI with commercial CH_3Li, was rinsed several times with ether in order to remove the lithium halide. The stoichiometry of these reactions was such as to ensure that there was no free methyllithium present; the halide content of the cuprate was less than 1% (by Volhard titration).

Cuprate Analysis. An aliquot of solution was removed from the reagent bottle and injected into a 50 or 100 mL volumetric flask containing 6 mL of 2 N hydrochloric acid, and a precipitate of cuprous iodide (identified by elemental analysis) was formed. The ether was evaporated on a steam bath, and 2 mL of 30% H_2O_2 (Baker) was added to oxidize the cuprous iodide (eq 6). The iodine liberated was sublimed

$$2H_2O_2 + 4H^+ + 2CuI \rightarrow 2Cu^{2+} + I_2 + 4H_2O \qquad (6)$$

by continued heating on the steam bath. A 6 M NaOH solution was added to neutralize the solution and drive the remaining I_2 out of solution. When the solution no longer contained iodine (failure to observe any purple gas upon heating the neutral solution with a Bunsen burner), it was cooled and diluted to the mark with concentrated ammonium hydroxide. The concentration of the resulting blue $Cu(NH_3)_4{}^{2+}$ solution was determined by measuring its absorbance at the λ_{max} of the complex, 610 nm, using a Beckman DU spectrophotometer and standard 1-cm quartz cells. The precision of duplicate analyses for copper content was ±2%.

Lithium Iodide. An aqueous solution of lithium iodide trihydrate was prepared from the reaction of Li_2CO_3 with 2 equiv of 47% aqueous HI. The volume of the resulting solution was reduced under vacuum. The concentrated solution was cooled in an ice bath, and the precipitate product was collected on a Büchner funnel, washed with several portions of ether, and dried over P_2O_5 at 110 °C for several days.

Mesityl Oxide (1). Mesityl oxide (Aldrich) was distilled through a 75 × 1.4-cm glass helices packed column, bp 63–64 °C (73mmHg) (lit.[46] 41 °C (23mmHg)). IR (film): 1695 (C=O), 1623 cm^{-1} (C=C). UV (ether): 231 (ϵ 10 550), shoulder at 325 nm (27).

Isophorone (3). Isphorone (Aldrich) was purified by vacuum distillation through a 75 × 1.4-cm glass helices packed column, bp 96–98 °C (20mmHg) (lit.[47] 99 °C (19mmHg)). IR (film): 1678, 1669 (C=O, d), 1638 cm^{-1} (C=C). UV (ether): 225 (ϵ 11 690), shoulder at 333 nm (29).

(+)-Pulegone (4). Pfaltz and Bauer (+)-pulegone was contaminated with a minor impurity (2–4% by gas chromatography). Pure material was obtained by preparative gas chromatography on a 8 ft × 0.25 in 10% Carbowax 20M on Chromosorb W (DMCS) column at 120 °C. IR (film): 1687 (C=O), 1626 cm^{-1} (C=C). UV (ether): 242 (ϵ 8640), shoulder at 325 nm (39).

2-Isopropylidenecyclopentanone (5). This compound was prepared by the method of Vavon and Apchie.[48] Fractional distillation of the product mixture gave 70.4 g (32%) of a pale yellow liquid, bp 86–90 °C (25mmHg) (lit.[48] 78–79 °C (10mmHg)). An oxime derivative of this ketone was prepared, mp 85–86.5 °C (lit.[48] 83 °C). IR (film): 1709 (C=O), 1632 cm^{-1} (C=C). ^{13}C NMR ($CDCl_3$): δ 19.45, 20.37, 24.52, 29.48, 40.58, 131.77, 147.28, 207.95.

2,5-Diisopropylidenecyclopentanone (6). 2-Isopropylidenecyclopentanone (3.0 g, 0.024 mol), acetone (20.0 g, 0.34 mol), and sodium methoxide (2.0 g, 0.037 mol) were dissolved in 15 g of methanol. This mixture was stirred at room temperature for 1.25 h and then maintained at reflux for 3.5 h. The reaction mixture was neutralized with acetic acid. After aqueous work-up the product was recrystallized from petroleum

---

(34) Smith, S. G.; Charbonneau, L. F.; Novak, D. P.; Brown, T. L. *J. Am. Chem. Soc.* **1972**, *94*, 7059.

(35) Billet, J.; Smith, S. G. *J. Am. Chem. Soc.* **1968**, *90*, 4108.

(36) Rudolph, S. E.; Charbonneau, L. F.; Smith, S. G. *J. Am. Chem. Soc.* **1973**, *95*, 7083.

(37) Hall, M. B.; Nester, R. G. *J. Opt. Soc. Am.* **1952**, *42*, 257.

(38) Alpert, D.; Bitzer, D. L. *Science (Washington, D.C.)* **1970**, *167*, 1582.

(39) Wiegers, K. E. Ph.D. Thesis, University of Illinois, Urbana, Illinois, 1977.

(40) Stifle, J. X-50 Report, CERL, University of Illinois, 1978.

(41) Bartlett, P. D.; Swain, C. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1941**, *63*, 3229.

(42) Vogel, A. I. *J. Chem. Soc.* **1943**, 636.

(43) Gilman, H.; Cartledge, F. K. *J. Organomet. Chem.* **1964**, *2*, 447.

(44) (a) Kauffman, G. B.; Pinnell, R. P. *Inorg. Synth.* **1960**, *6*, 3. (b) Keller, R. N.; Wycoff, H. D. *Ibid.* **1946**, *2*, 1.

(45) Novak, D. P. Ph.D. Thesis, University of Illinois, Urbana, Illinois, 1971.

(46) Stross, F. H.; Monger, J. M.; Finch, H. d. V. *J. Am. Chem. Soc.* **1947**, *69*, 1627.

(47) Baker, J. W. *J. Chem. Soc.* **1926**, 663.

(48) Vavon, M. G.; Apchie, A. *Bull. Soc. Chim. Fr.* **1928**, 667.

ether (bp 35–60 °C), yielding 1.08 g (27%) of 2,5-diisopropylidenecyclopentanone, mp 31–38 °C. This material was sublimed at room temperature and 0.2 mm to yield 0.42 g of pure product, mp 39.5–41 °C (lit.[48] 41 °C).

Dypnone (7). This compound was prepared by the self-condensation of acetophenone in the presence of aluminum *tert*-butoxide.[49] Fractional distillation of the product mixture gave 29.9 g (54%) of a yellow liquid, bp 138–140 °C (0.3mmHg) (lit.[50] 172 °C (1mmHg)). This product was contaminated (10% by NMR) with presumably the cis isomer. Equilibration of an ethereal solution of the enone with a trace amount of *p*-toluenesulfonic acid or an ethanolic solution of the enone with a trace amount of hydrochloric acid reduced the impurity to 5%. The ketone was further purified by chromatography on a neutral aluminum oxide (Brinkmann) column, eluting with benzene. IR (film): 1652 (C=O), 1590 cm^{-1} (C=C). UV (ether): 288 (ϵ 17 460), shoulder at 350 nm (250).

3,3-Dimethylacryloyl Chloride. Acrylic acid (50 g, 0.50 mol) was dissolved in thionyl chloride (44 mL, 0.60 mol). The solution was maintained at reflux for 1.3 h, stirred at room temperature for 2.5 h, and then maintained at reflux an additional 1 h. The product was fractionally distilled at 72.5–75 °C (50mmHg) (lit.[51] 59–61 °C (30mmHg)), yielding 54.8 g (92%) of 3,3-dimethylacryloyl chloride.

1-Phenyl-3-methyl-2-buten-1-one (2a). This compound was prepared by the method of House, Prabhu, Wilkins, and Lee[29] in 26% yield. The material was purified by chromatography on silica gel, eluting with a 1:1 mixture of methylene chloride and cyclohexane, followed by chromatography on silica gel with petroleum ether eluant. The product was distilled at 82 °C (0.6mmHg) (lit.[52] 120–121 °C (4mmHg)). IR (film): 1664 (C=O), 1618 cm^{-1} (C=C). UV (ether): 257 nm (ϵ 26 500).

Substituted 1-Phenyl-3-methyl-2-buten-1-ones. Ketones **2b–e** were prepared by the reaction of the corresponding substituted arylcadmium reagent with 3,3-dimethylacryloyl chloride.[53] The arylmagnesium bromide was prepared from the reaction of the corresponding substituted aryl bromide (0.27 mol) with magnesium turnings (6.7 g, 0.28 mol) in dry diethyl ether. The Grignard solution was cooled in an ice bath, cadmium chloride (ground thoroughly and dried at 110 °C; 26.5 g, 0.15 mol) was added over a 10-min period, and the resulting mixture was heated at reflux with stirring for 1 h. Most of the ether was then removed and replaced with dry benzene (distilled from $LiAlH_4$). A solution of 3,3-dimethylacryloyl chloride (25.6 g, 0.22 mol) in 50 mL of benzene was added to the cadmium reagent at room temperature, and the mixture was heated at reflux for 1 h. The reaction mixture was cooled in an ice bath, and the salts were decomposed with 20% sulfuric acid and worked up in the usual fashion. The product was fractionally distilled, chromatographed, and then redistilled. Below are listed the yields (after the initial distillation), chromatography conditions, boiling or melting points, NMR spectra (new compounds only), prominent IR absorptions, UV spectra, and elemental analyses (new compounds only) of ketones **2b–e**.

1-(4-Phenoxyphenyl)-3-methyl-2-buten-1-one (2b): 53% yield; chromatographed on silica gel with 1:4 petroleum ether–methylene chloride; bp 162 °C (0.55mmHg); NMR (CCl_4) δ 1.93 (s, 3 H), 2.12 (s, 3 H), 6.47 (m, 1 H), 6.67–7.43 (m, 7 H), 7.50–7.87 (m, 2 H); IR (film) 1664 (C=O), 1626 cm^{-1} (C=C); UV (ether) 276 nm (ϵ 22 600).

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.67; H, 6.19.

1-(4-Methylphenyl)-3-methyl-2-buten-1-one (2c): 50% yield; chromatographed on silica gel with methylene chloride; bp 90–92 °C (0.9mmHg) (lit.[54] 55–60 °C (0.15mmHg)); IR (film) 1662 (C=O), 1613 cm^{-1} (C=C); UV (ether) 261 nm (ϵ 21 400).

1-(4-Chlorophenyl)-3-methyl-2-buten-1-one (2d): 43% yield; chromatographed on silica gel with 9:1 methylene chloride–petroleum ether; mp 40.5–42 °C after two recrystallizations from petroleum ether (lit.[54] 37.5–38.5 °C); IR (KBr) 1667 (C=O), 1627 cm^{-1} (C=C); UV (ether) 264 nm (ϵ 23 900).

1-(3-(Trifluoromethyl)phenyl)-3-methyl-2-buten-1-one (2e): 40% yield; chromatographed on silica gel with 1:1 methylene chloride–cyclohexane; bp 90–91 °C (0.8mmHg); NMR (CCl_4) δ 2.03 (s, 3 H), 2.20 (s, 3 H), 6.65 (m, 1 H), 7.36–7.83 (m, 2 H), 7.93–8.15 (m, 2 H); IR (film) 1668 (C=O), 1625 cm^{-1} (C=C); UV (ether) 254 nm (ϵ 17 300).

Anal. Calcd for $C_{12}H_{11}F_3O$: C, 63.16; H, 4.86; F, 24.98. Found: C, 62.87; H, 4.57; F, 24.62.

Chalcone (8a). This material was recrystallized from ethanol and then dried over P_2O_5 at 39 °C, mp 57.5–58 °C (lit.[55] 58 °C). IR (KBr): 1669 (C=O), 1614 cm^{-1} (C=C). UV (ether): 302 nm (ϵ 24 200).

4-Methoxychalcone (8b). This material was the generous gift of Mr. Rick Gdanski. It was recrystallized from ethanol and dried over P_2O_5 at 65 °C, mp 73.5–75 °C (lit.[56] 77–78, 74 °C). IR (KBr): 1662 (C=O), 1604 cm^{-1} (C=C). UV (ether): 328 nm (ϵ 25 300).

4-Methylchalcone (8c). Freshly distilled *p*-tolualdehyde (15.0 g, 0.13 mol), freshly distilled acetophenone (15.0 g, 0.13 mol), sodium hydroxide (6.4 g, 0.16 mol), and 150 mL of 50% aqueous ethanol were stirred at reflux for 4 h. The reaction mixture was cooled in an ice bath and then filtered to yield 27.3 g (98%) of 4-methylchalcone. This material was recrystallized from ethanol and then dried over P_2O_5 at 78 °C, yielding a pale yellow solid, mp 95.5–97 °C (lit.[57] 96.4 °C). IR (KBr): 1660 (C=O), 1603 cm^{-1} (C=C). UV (ether): 312 nm (ϵ 27 000).

4-Chlorochalcone (8d). This material was recrystallized from ethanol and then dried over P_2O_5 at 100 °C, mp 113.5–115 °C (lit.[58] 114–115 °C). IR (KBr): 1660 (C=O), 1603 cm^{-1} (C=C). UV (ether): 306 nm (ϵ 27 800).

3-(Trifluoromethyl)benzaldehyde. This compound was prepared from the acid hydrolysis of the corresponding acetal, which was prepared by the addition of 3-(trifluoromethyl)phenylmagnesium bromide to triethyl orthoformate in diethyl ether solvent. The sodium bisulfite addition product was formed in order to purify the crude product, and the aldehyde was regenerated by slowly adding a saturated $NaHCO_3$ solution to the solid. Distillation of the product yielded 7.15 g (12%) of a colorless liquid, bp 39–43 °C (0.8mmHg), which rapidly underwent air oxidation. It was used immediately in the preparation of 3-(trifluoromethyl)chalcone.

3-(Trifluoromethyl)chalcone (8e). Freshly prepared 3-trifluoromethylbenzaldehyde (6.9 g, 0.40 mol), freshly distilled acetophenone (4.8 g, 0.04 mol), sodium hydroxide (2.1 g, 0.051 mol), and 60 mL of 50% aqueous ethanol were stirred at reflux for 2.5 h. The reaction mixture was cooled in an ice bath and then filtered to yield 10.9 g (95%) of 3-trifluoromethylchalcone. This material was recrystallized from ethanol and then dried over P_2O_5 at 100 °C to yield a pale yellow solid, mp 108.5–109.5 °C (lit.[58] 106–108 °C). IR (KBr): 1668 (C=O), 1613 cm^{-1} (C=C). UV (ether): 293 nm (ϵ 24 900).

Product Analyses. The conjugate addition reaction of lithium dimethylcuprate with each of the ketones studied was carried out on a larger scale, and the products were analyzed by NMR and GC. In each case, the NMR spectrum of the product was consistent with the structure of the expected conjugate addition product, and no extraneous NMR signals were observed. Each compound exhibited a single peak upon gas chromatographic analysis, except that the product obtained from (+)-pulegone exhibited two GC peaks, due to the diastereomeric ketones formed upon conjugate addition of $(CH_3)_2CuLi$. The NMR signals of the *tert*-butyl and methyl protons in each of the diastereomers were resolved in the presence of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III) (obtained from Aldrich), and the integrated areas of the two *tert*-butyl signals were in close agreement with the integrated areas of the two peaks observed in the gas chromatograph. The products from these reactions were obtained in 90–100% yield.

2,2,6,6-Tetramethylcyclohexanone (9). This material was prepared by Dr. J. W. Wheeler by exhaustive methylation of cyclohexanone. IR (film): 1699 cm^{-1} (C=O).

After this compound was treated with lithium dimethylcuprate in the stopped-flow apparatus for ca. 5 min, the effluent was quenched in water and worked up in the usual manner. Gas chromatographic analysis of the product revealed that it contained only unreacted 2,2,6,6-tetramethylcyclohexanone.

Acknowledgment. This work was supported by the National Science Foundation and donors of the Petroleum Research Fund, administered by the American Chemical Society. One of us (S.R.K.) gratefully acknowledges receipt of a University of Illinois Fellowship (1975–1976). The authors wish to thank Dr. Karl E. Wiegers for many helpful discussions and Mr. Raul M. Oteiza for his assistance in modifying and maintaining the instruments used in this study.

---

(49) Wayne, W.; Adkins, H. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. 3, p 367.

(50) Lutz, R. E.; Slade, L. T. *J. Org. Chem.* **1961**, *26*, 4888.

(51) Wolfrom, M. L.; Cooper, P. W. *J. Am. Chem. Soc.* **1949**, *71*, 2668.

(52) Braude, E. A.; Coles, J. A. *J. Chem. Soc.* **1950**, 2012.

(53) (a) Carson, J.; Prout, F. S. *Org. Synth.* **1948**, *28*, 75. (b) Nightingale, D.; Wadsworth, F. *J. Am. Chem. Soc.* **1945**, *67*, 416. (c) Shirley, D. A. *Org. React.* (*N.Y.*) **1954**, *8*, 28.

(54) Watson, J. M.; Irvine, J. L.; Roberts, R. M. *J. Am. Chem. Soc.* **1973**, *95*, 3348.

(55) Adams, R.; Kern, J. W.; Shriner, R. L. "Organic Syntheses"; Wiley: New York, 1941; Collect. Vol. 1, p 101.

(56) Pond, F. J.; Shoffstall, A. S. *J. Am. Chem. Soc.* **1900**, *22*, 658.

(57) Hanzlik, V.; Bianchi, A. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 2282.

(58) Szmant, H. H.; Basso, A. J. *J. Am. Chem. Soc.* **1952**, *74*, 4397.