ice–acetone bath to an ice bath and 1 g of 1,2,3-trimethylbenzene was added. The reaction mixture was left at 0 °C for 48 h. The reaction with trimethylchlorosilane or borane was carried out as described before.

^{1}H NMR spectra in the presence of Eu(fod)$_3$ were recorded by adding small portions of this shift reagent to CCl_4 solutions of the samples in NMR tubes until well resolved spectra were obtained and further addition had no significant influence on the spectra. (Excess must be avoided, since considerable broadening is obtained.)

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Kinetics and Mechanism of Lithium Aluminum Hydride and Lithium Alkoxyaluminohydride Reductions of Ketones in Diethyl Ether

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Received August 20, 1976

Abstract: The kinetics of reaction of the ketones 2,4,6-trimethylbenzophenone, 2,2′-diethylbenzophenone, and 2,2′-dimethylbenzophenone with excess lithium aluminum hydride and lithium *tert*-butoxyaluminohydrides were studied by stopped-flow UV spectroscopy in diethyl ether solution at 25.0 °C. Under these conditions, the reductions are first order in ketone, but the kinetic orders in stoichiometric lithium aluminum hydride range from 0.5 to 0.6, indicating participation by both monomeric and dimeric lithium aluminum hydride. Kinetic isotope effects measured for reductions using $LiAlD_4$ in ether correspond to k_H/k_D values of 1.3–1.4. The rates of reduction by $LiAlH_4$ of substituted 2,4,6-trimethylbenzophenones were correlated with σ constants and yielded a value for ρ of +1.95. The kinetics of ketone reductions with lithium *tert*-butoxyaluminohydrides are consistent with disproportionation of the alkoxide species.

Since the initial discovery of lithium aluminum hydride in 1947,[2] thousands of applications of this powerful reducing agent have been reported.[3] The formulation of detailed mechanisms for the reduction of ketones by lithium aluminum hydride and its alkoxy derivatives[4] in ether solvents has been impeded by the paucity of kinetic data for these very fast reactions and by a lack of information regarding the structure and composition of these reagents in solution.

Recently Ashby and co-workers[5,6] reported association data for several complex metal hydrides and their alkoxy derivatives in diethyl ether and tetrahydrofuran (THF). Between 0.1 and 0.45 *m*, the association *i* value for $LiAlH_4$ in ether varies from 1.75 to 2.2,[5,7] but $LiAlH_4$ exists as ion pairs or triple ions in THF.[6] Unfortunately, no association measurements were carried out on the alkoxy derivatives of $LiAlH_4$ in ether.

Since the original preparation of lithium tri-*tert*-butoxy-

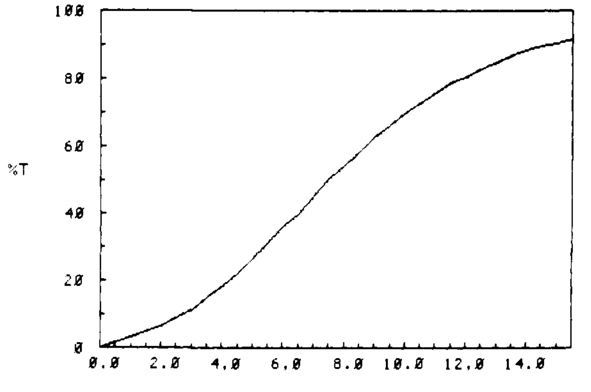


Figure 1. Plot of percent transmission vs. time for the reaction of 1.00 × 10^{-3} M ketone **1a** with 8.6 × 10^{-3} M $LiAlH_4$ in diethyl ether at 25.0 °C measured at 280 nm.

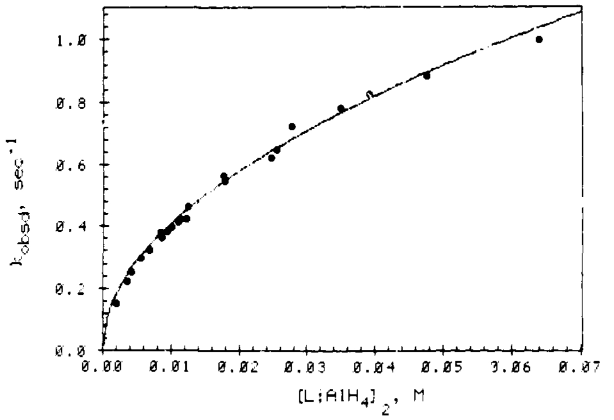


Figure 2. Plot of k_{obsd} vs $[LiAlH_4]_2$ for reduction of ketone **1a** in ether at 25.0 °C. The line was calculated from eq 2.

aluminohydride,[8] this and related reagents have received much attention as selective reducing agents.[4,9,10] It has been found that $LiAl(O\text{-}t\text{-}Bu)_3H$, which is only slightly soluble in diethyl ether,[8] will reduce ketones at measurable rates in THF or diglyme.[11,12] The stereoselectivity of $LiAl(O\text{-}t\text{-}Bu)_3H$ in ketone reductions often differs considerably from that of lithium aluminum hydride itself, which has been attributed to the presumably greater steric bulk of the tri-*tert*-butoxy species.[9,13-15] However, lithium trimethoxyaluminohydride is actually *more* selective than $LiAl(O\text{-}t\text{-}Bu)_3H$ in many instances.[13,15,16]

In 1962, Haubenstock and Eliel[15] proposed that alkoxyaluminohydrides formed as intermediates in the reduction of 3,3,5-trimethylcyclohexanone with $LiAlH_4$ in ether do not themselves serve as reducing agents, but disproportionate to insoluble $LiAl(OR)_4$ and $LiAlH_4$ as soon as they are formed, e.g.

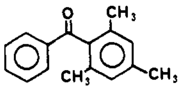
$$4LiAlH_3(OR) \rightarrow 3LiAlH_4 + LiAl(OR)_4 \qquad (1)$$

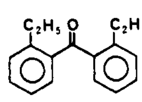
Thus, hydride transfer is considered to take place only from $LiAlH_4$ itself during the reduction of ketones. Additional studies[8,13,17] have supported the concept of disproportionation of alkoxyaluminohydrides containing secondary alkoxide ligands, but it has been reported[8,15-17] that $LiAl(OCH_3)_3H$ and $LiAl(O\text{-}t\text{-}Bu)_3H$ do not undergo disproportionation. However, Kader's NMR studies[18] suggest that rapid ligand exchange or disproportionation is indeed feasible in the lithium *tert*-butoxyaluminohydride system.

While many kinetic studies have been performed on the reactons of sodium borohydride with ketones, kinetic data for reductions using aluminohydrides are rather scarce. The rates of reduction of ketones by sodium borohydride[19] and the products of ketone reductions with aluminohydrides and alkoxyaluminohydrides[13,16,20,21] are very sensitive to steric hindrance about the carbonyl group. Kinetic isotope effects measured for ketone reductions with $NaBD_4$ have been found to be small and inverse, suggesting that a small primary isotope effect is dominated by an inverse secondary effect of the three deuterium atoms not being transferred in the transition state.[22-24]

Rate studies involving the competitive reduction of alkyl-substituted cyclohexanones by aluminohydrides have been conducted by Eliel and Senda.[13] The kinetics of reaction of 2,4,6-trimethylbenzophenone (**1a**) with $LiAlH_4$ in THF were reported to be first order in ketone and first order in hydride.[25] The rates of reduction of substituted benzophenones[11] and cyclohexanones[12] by $LiAl(O\text{-}t\text{-}Bu)_3H$ have been measured and found to be first order in ketone and first order in hydride. Wigfield measured an inverse primary isotope effect in the reduction of the highly hindered 3,3,5,5-tetramethylcyclohexanone with $LiAl(O\text{-}t\text{-}Bu)_3D$.[26]

This paper reports the results of kinetic studies of the reduction of 2,4,6-trimethylbenzophenone (**1a**), 2,2′-diethylbenzophenone (**2**), and 2,2′-dimethylbenzophenone (**3**) by lithium aluminum hydride and lithium *tert*-butoxyaluminohydrides in diethyl ether, measured by stopped-flow ultraviolet spectroscopy.


1a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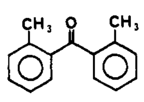
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Results

Reduction of Ketones by $LiAlH_4$ in Ether. The rate of disappearance of 2,4,6-trimethylbenzophenone (**1a**) was measured by stopped-flow UV spectroscopy at 25.0 °C in diethyl ether solution at ketone concentrations of (0.25–3.0)× 10^{-3} M and $LiAlH_4$ concentrations of 3 × 10^{-3}–0.13 M. A typical plot of percent transmission vs. time, under the pseudo-first-order conditions of excess hydride used in these experiments, is illustrated in Figure 1. In all cases excellent adherence to a first-order rate law was observed throughout a kinetic run, with standard plots linear through at least 5 half-lives. In addition to displaying first-order kinetics within a given reaction, the measured rate constants were appropriately independent of initial ketone concentration.

The dependence of the observed pseudo-first-order rate constants upon the concentration of lithium aluminum hydride (predominantly dimeric over this concentration range[5,7]) is nonlinear (Figure 2). A plot of log (k_{obsd}) vs. log ($[LiAlH_4]_2$) is linear, with slope 0.53 (r = 0.998), indicating that the reduction is approximately one-half order in dimeric $LiAlH_4$. As summarized in Table I, these data are accurately described by the rate law:

$$-d[\text{ketone}]/dt = k_1[LiAlH_4]_2^{1/2}[\text{ketone}] \qquad (2)$$

where $k_1 = k_{obsd}/[LiAlH_4]_2^{1/2}$. The average value of k_1 obtained in this way is a constant 4.1 ± 0.2 $M^{-1/2}\,s^{-1}$.

The rate of reduction of ketone **2** under comparable conditions also exhibits a nonlinear dependence upon $[LiAlH_4]_2$ (Figure 3). However, in this case a plot of log (k_{obsd}) vs. log ($[LiAlH_4]_2$) has a slope of 0.60 (r = 0.992), and the values obtained by dividing k_{obsd} by $[LiAlH_4]_2^{1/2}$ are not constant (Table II). These data are consistent with reduction proceeding predominantly via monomeric $LiAlH_4$, but with an additional contribution to the rate from reduction by the dimer:

Table I. Summary of Rate Constants for the Reaction of $LiAlH_4$ with ca. 5×10^{-4} M 2,4,6-Trimethylbenzophenone in Ether at 25.0 °C

$10^2 [LiAlH_4]_2$, M	k_{obsd}, s^{-1} [a]	k_1, $M^{-1/2} s^{-1}$
0.17	0.15	3.7
0.35	0.22	3.8
0.41	0.26	4.0
0.55	0.30	4.0
0.67	0.33	4.0
0.82	0.38	4.2
0.83	0.37	4.0
0.93	0.39	4.0
0.98	0.40	4.1
1.08	0.42	4.1
1.10	0.43	4.1
1.21	0.43	3.9
1.23	0.47	4.3
1.8	0.57	4.3
1.8	0.55	4.2
2.5	0.65	4.1
2.8	0.73	4.4
3.5	0.79	4.2
3.9	0.83	4.2
4.7	0.89	4.1
6.4	1.00	4.0
		Ave 4.1 ± 0.2

[a] Each rate constant is the average of four kinetic runs.

Table II. Summary of Rate Constants for the Reaction of $LiAlH_4$ with ca. 1×10^{-3} M 2,2′-Diethylbenzophenone in Ether at 25.0 °C

$10^2[LiAlH_4]_2$, M	k_{obsd}, s^{-1} [a]	$10^{-1}k$, $M^{-1/2} s^{-1}$
0.18	25	58
0.55	57	77
0.56	59	79
0.59	60	78
0.62	61	78
0.67	61	74
0.72	62	73
0.94	73	75
1.05	85	83
1.08	80	77
1.15	86	80
1.23	87	78
1.30	97	85
1.38	108	92
1.48	103	85
1.90	114	83
1.94	120	86
2.02	120	85
2.17	130	90
2.21	125	84
2.64	140	87
3.38	150	82
3.50	160	86
3.81	170	88
4.17	170	83

[a] Each rate constant is the average of four kinetic runs.

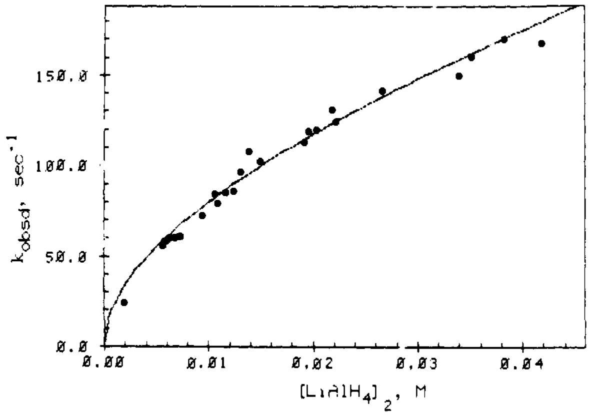


Figure 3. Plot of k_{obsd} vs. $[LiAlH_4]_2$ for reduction of ketone **2** in ether at 25.0 °C. The line was calculated from eq 3.

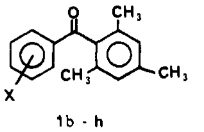
$$-d[\text{ketone}]/dt = \{k_1[LiAlH_4]_2^{1/2} + k_2[LiAlH_4]_2\} \times [\text{ketone}] \quad (3)$$

The experimental data are adequately described by values of k_1 and k_2 of 720 and 775 $M^{-1} s^{-1}$, respectively (Figure 3). Similarly, the log-log plot for the reduction of ketone **3** exhibits a slope of 0.59 ($r = 0.992$), again indicating the dependence of the pseudo-first-order rate constant upon the concentrations of both monomeric and dimeric $LiAlH_4$. These data are fit using $k_1 = 4100\ M^{-1/2} s^{-1}$ and $k_2 = 4150\ M^{-1} s^{-1}$ (Figure 4). The rates of reduction of ketones **2** and **3** with $LiAlH_4$ are also independent of initial ketone concentration. In each case the sole product isolated from these reactions was the expected benzhydrol.

Reduction of Ketones by $LiAlD_4$ in Ether. The rates of reaction of ketones **1a**, **2**, and **3** with $LiAlD_4$ in ether were measured at several concentrations of $LiAlD_4$. The calculated kinetic isotope effects are shown in Table III.

The reduction of ketone **1a** with $LiAlD_4$ was also performed on a preparative scale and the product isolated in 94.4% yield. The ^1H NMR spectrum of the product was identical with that of authentic 2,4,6-trimethylbenzhydrol-d_0, except that the one-proton singlet at δ 6.28 was absent. The aromatic resonances at δ 6.84 and 7.25 integrated in a ratio of 5:2, indicating that, within the limits of sensitivity of the NMR experiment (ca. 5%), the deuterium atom had been transferred exclusively to the carbonyl carbon.

Substituent Effects on Rate of Reduction of 2,4,6-Trimethylbenzophenone. Seven derivatives of 2,4,6-trimethylbenzophenone possessing substituents in the phenyl ring (**1b–1h**) were reduced by $LiAlH_4$ in ether at 25.0 °C. The pseudo-first-order rate constants for disappearance of the ketone were correlated with Hammett σ constants.[27] A plot of log (k_X/k_H) vs. σ (Figure 5) was linear with slope (ρ) = +1.95 ± 0.1 ($r = 0.993$).



1b - h

1b, X = p-OCH_3
c, X = p-CH_3
d, X = p-Cl
e, X = p-Br
f, X = m-Cl
g, X = m-CF_3
h, X = p-CF_3

Reduction of Ketones by Lithium Alkoxyaluminohydrides. The kinetics of reaction of ketones **1a**, **2**, and **3** with a series of reagents prepared by adding various quantities of dry *tert*-butyl alcohol to stock solutions of $LiAlH_4$ in ether were measured. The observed pseudo-first-order rate constants decrease markedly as the molar ratio [*t*-BuOH]:[$LiAlH_4$] increases from 0 to 3. The variation in k_{obsd} with the [*t*-BuOH]:[$LiAlH_4$] molar ratio is seen for ketones **1a**, **2**, and **3** in Figures 6, 7, and 8, respectively. Each reaction displayed good first-order kinetics within a run.

The rates of reduction of ketone **1a** by alkoxide solutions prepared from $LiAlH_4$ and added **1a** were also measured as a function of the molar ratio of addend to stoichiometric

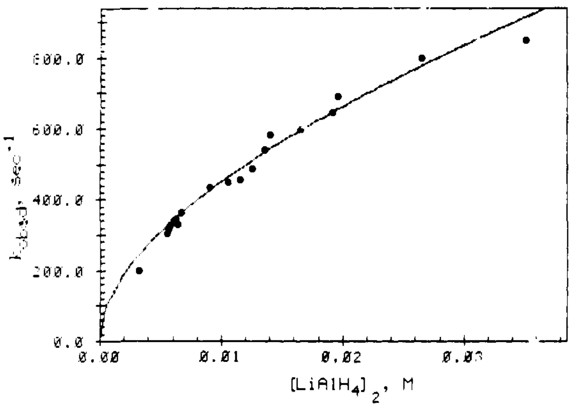


Figure 4. Plot of k_{obsd} vs. $[LiAlH_4]_2$ for reduction of ketone **3** in ether at 25.0 °C. The line was calculated from eq 3.

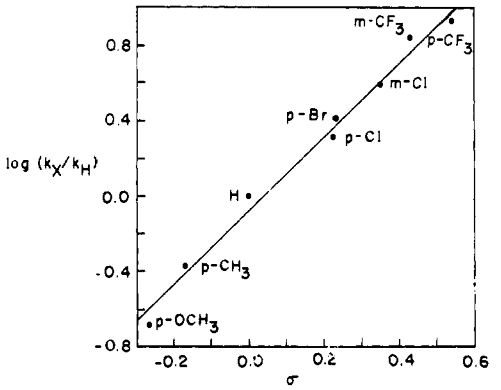


Figure 5. Comparison of specific rates for reduction of substituted 2,4,6-trimethylbenzophenones (ca. 5 × 10^{-4} M) by 0.049 M $LiAlH_4$ in ether with σ constants.

Table III. Kinetic Isotope Effects for the Reduction of Ketones **1a**, **2**, and **3** with $LiAlD_4$ in Ether at 25.0 °C

Ketone	$10^3[LiAlD_4]_2$, M	k_H/k_D	Ave
1a	1.98	1.43	
	4.14	1.46	
	6.89	1.28	1.40
2	1.98	1.41	
	4.14	1.31	
	6.89	1.19	1.30
3	1.98	1.44	
	4.14	1.33	
	6.89	1.19	1.32

$LiAlH_4$. The rate constants again decrease markedly with increasing molar ratio, but the quantitative shape of the curve differs from that obtained using *tert*-butyl alcohol as the added ligand.

In an additional probe into the effects of alkoxides on the rate of reduction of ketone **1a**, a solution was prepared by distilling ether onto a mixture of 5.26 mmol of solid $LiAlH_4$ and 5.00 mmol of solid $LiAl(O\text{-}t\text{-}Bu)_3H$. The ratio of the rate constant for reduction of **1a** by the resulting hydride solution, compared with the rate constant for $LiAlH_4$ alone at the same concentration of total aluminum, was calculated to be 0.2.

Discussion

Mechanism of Reduction of Substituted Benzophenones by $LiAlH_4$ in Ether. The observation that reduction of the highly hindered 2,4,6-trimethylbenzophenone (**1a**) is approximately one-half order in lithium aluminum hydride in ether solution is reminiscent of the fractional orders often observed for the reactions of highly associated organolithium reagents with ketones.[28] Such kinetic results have been interpreted to indicate that the predominant reaction is by way of monomeric reagent in equilibrium with the aggregated species. The knowledge[5,7] that $LiAlH_4$ is predominantly dimeric in ether below 0.5 M thus suggests that hydride transfer from the $LiAlH_4$ monomer is the dominate mode of reduction of **1a** (Scheme I). Indeed, the accuracy of the one-half-order dependence on $[LiAlH_4]$ of the kinetic data for ketone **1a** supports the contention that $LiAlH_4$ is dimeric in ether. The calculated rate constant k_1 of 4.1 $M^{-1/2}\,s^{-1}$ (Table I) is equal to the actual second-order rate constant, k, times the square root of the equilibrium constant for dissociation of the $LiAlH_4$ dimer, K. The value of this equilibrium constant is not known.

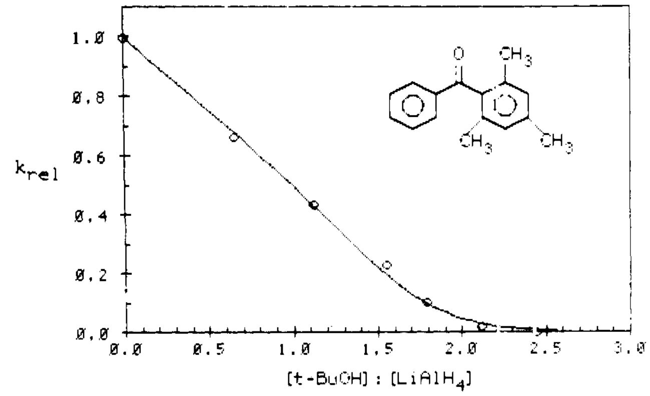


Figure 6. Plot of k_{rel} vs. $[t\text{-}BuOH]:[LiAlH_4]$ for reduction of **1a** (4.23 × 10^{-4} M). Initial $LiAlH_4$ concentration = 0.0242 M. The line is calculated from eq 7.

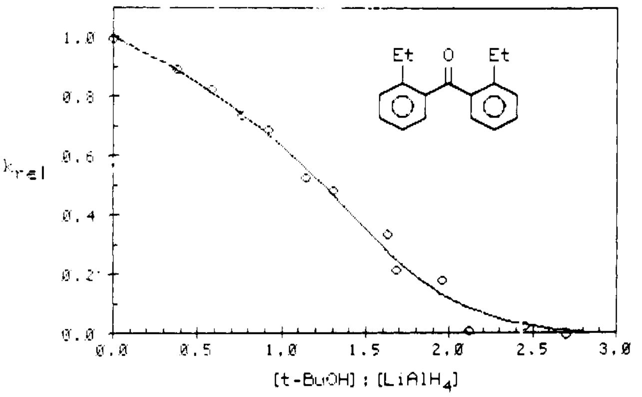


Figure 7. Plot of k_{rel} vs. $[t\text{-}BuOH]:[LiAlH_4]$ for reduction of **2** (ca. 5 × 10^{-4} M). Initial $LiAlH_4$ concentrations ca. 0.025 M. The line is calculated from eq 7.

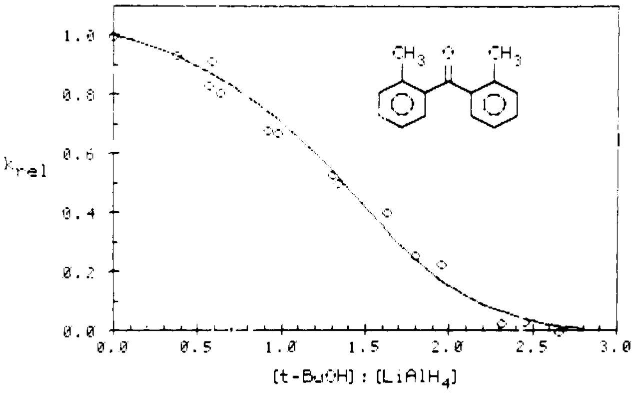


Figure 8. Plot of k_{rel} vs. $[t\text{-}BuOH]:[LiAlH_4]$ for reduction of **3** (ca. 7 × 10^{-4} M). Initial $LiAlH_4$ concentrations ca. 0.025 M. The line is calculated from eq 7.

Table IV. Rate Constants for Reduction of Ketones **1a**, **2**, and **3** by Monomeric and Dimeric $LiAlH_4$ in Ether at 25.0 °C

Ketone	k_1, $M^{-1/2}\ s^{-1}$	k_2, $M^{-1}\ s^{-1}$
1a	4.1	0
2	720	775
3	4100	4150

Scheme I

$$(LiAlH_4)_2 \overset{K}{\rightleftharpoons} 2\ LiAlH_4$$

$$LiAlH_4 + \text{ketone} \xrightarrow{k} \text{products}$$

$$\begin{aligned} -d[\text{ketone}]/dt &= kK^{1/2}[LiAlH_4]_2{}^{1/2}[\text{ketone}] \\ &= k_1[LiAlH_4]_2{}^{1/2}[\text{ketone}] \end{aligned} \quad (4)$$

Reductions of the less hindered ketones **2** and **3** exhibit a significantly higher apparent order in lithium aluminum hydride than does the reduction of **1a**, suggesting that the reaction proceeds through both monomeric and dimeric $LiAlH_4$ (Scheme II). The rate law derived for this mechanism is eq 3, in which $k_1 = kK^{1/2}$. The rate constants obtained by computer fitting of the kinetic data for ketones **1a**, **2**, and **3** are summarized in Table IV. It is not possible to directly compare the magnitudes of k_1 and k_2 for a given ketone, as k_1 includes the value for the dimer-monomer equilibrium constant for $LiAlH_4$, but a calculation of the relative contributions to k_{obsd} from each pathway indicates that the dimer of $LiAlH_4$ never accounts for more than about 20% of the total reaction for **2** and **3**, under the conditions used in these experiments.

Scheme II

$$(LiAlH_4)_2 \overset{K}{\rightleftharpoons} 2LiAlH_4$$

$$LiAlH_4 + \text{ketone} \xrightarrow{k} \text{products}$$

$$(LiAlH_4)_2 + \text{ketone} \xrightarrow{k_2} \text{products}$$

Qualitatively, the curved rate plots observed for the reductions of ketones **1a**, **2**, and **3** (Figures 2–4) could also result from the transformation of a significant fraction of the ketone into an intermediate complex with $LiAlH_4$. Such a mechanism has been invoked in the reaction of Grignard reagents with ketones in ether.[29] However, unlike the Grignard reaction, which exhibits new ultraviolet and infrared absorbances attributed to a complex between reactants, within the accuracy of our rapid scan measurements of the reaction between ketone **2** and $LiAlH_4$ in ether, no perturbation of the ketone spectrum was observed. Although the reaction may actually go through a complex between reactants, neither the kinetic data nor the spectroscopic studies require accumulation of such an intermediate under the reaction conditions employed in these experiments.

The possibility was considered that the addition of hydride to the highly hindered ketone **1a** might be proceeding via initial conjugate 1,4- or 1,6-addition to one of the aromatic rings, followed by tautomerization to the final product. Therefore, **1a** was reduced with $LiAlD_4$ in ether and the product isolated. A conjugate addition mechanism could result in partial deuterium incorporation into the phenyl ring, as well as partial labeling at the carbinyl position. However, the proton NMR spectrum of the reaction product showed the deuterium to be present (ca. 5% accuracy) only at the carbinyl position, indicating that conjugate addition of hydride is not a major reaction pathway in the reduction of **1a**.

The kinetic isotope effects reported in Table III for the $LiAlD_4$ reduction of ketones **1a**, **2**, and **3** are a composite of both primary and secondary effects for reduction by $LiAlH_4$ monomer and by $LiAlH_4$ dimer. The small magnitudes of the isotope effects are consistent with the concept of a reactant-like transition state, as suggested by the Hammond postulate for such an exothermic reaction. However, a kinetic isotope effect of this magnitude may also be obtained if the reaction involves a product-like transition state.[30]

The ρ value of +1.95 obtained for reduction of ketones **1a–h** by $LiAlH_4$ in ether is very similar to the ρ value of +2.13 measured for reduction of some para,para′-disubstituted benzophenones by $LiAl(O\text{-}t\text{-}Bu)_3H$ in THF.[11] Both of these values are considerably smaller than those measured for sodium borohydride reductions of substituted fluorenones (+2.65[31a] and +3.06[31b]) and acetophenones (+2.6[32a] and +3.06[32b]). These data are all consistent with the proposal[33] that the transition states for ketone reductions with aluminohydrides are much more reactant-like than are the transition states for ketone reductions with borohydrides.

Mechanism of Reduction of Substituted Benzophenones by Lithium *tert*-Butoxyaluminohydrides in Ether. The role of alkoxides in ketone reductions by $LiAlH_4$ and $LiAl(OR)_nH_{4-n}$ has not been clearly understood. It is of interest to consider the kinetic results of the reduction of a ketone with a series of reagents containing different molar ratios of an alcohol, ROH, to lithium aluminum hydride ([ROH]:[$LiAlH_4$]). A limiting case may be envisioned regarding the effects of disproportionation of alkoxyaluminohydrides upon the shape of a plot of k_{rel} vs. [ROH]: [$LiAlH_4$], in which pseudo-first-order rate constants are divided by the rate constant for $LiAlH_4$ alone at the concentration of total aluminum used in order to obtain k_{rel}. Partial disproportionation of alkoxides, with one or more reactive hydride species, will result in plots of k_{rel} vs. [ROH] [$LiAlH_4$] which are curved, with no sharply defined x intercept. The kinetics observed when ketones **1a–3** are reduced with a series of lithium *tert*-butoxyaluminohydrides are consistent with this behavior.

The disproportionation equilibria have been considered to involve the following stages:

$$4LiAl(O\text{-}t\text{-}Bu)H_3 \overset{K_1}{\rightleftharpoons} (LiAlH_4)_2 + 2LiAl(O\text{-}t\text{-}Bu)_2H_2 \quad (5)$$

$$2LiAl(O\text{-}t\text{-}Bu)_2H_2 \overset{K_2}{\rightleftharpoons} LiAl(O\text{-}t\text{-}Bu)H_3 + LiAl(O\text{-}t\text{-}Bu)_3H \quad (6)$$

It is not necessary to consider the effects of further disproportionation of $LiAl(O\text{-}t\text{-}Bu)_3H$, because $LiAl(O\text{-}t\text{-}Bu)_4$ cannot be formed in ether.[8]

Because of the lack of data on the state of aggregation of the alkoxyaluminohydrides, these equations represent the alkoxy species as monomers and lithium aluminum hydride as a dimer. Based on these assumptions, the equilibrium concentrations of all hydride species present at any molar ratio of [t-BuOH]: [$LiAlH_4$] may be estimated from eq 5 and 6 for any specified pair of equilibrium constants K_1 and K_2. The resulting concentrations may be used to calculate k_{rel} at that molar ratio, by dividing k_{calcd} (eq 7) by k_{obsd} for $LiAlH_4$ alone at the same concentration of total aluminum. By having the hydride present in large excess over the ketone, not enough hydride is consumed in the kinetics experiment to significantly perturb the equilibrium concentrations of aluminohydride species, and it is possible to probe the kinetic behavior of the equilibrium distribution of reducing agents.

$$\begin{aligned} k_{calcd} = k_1[LiAlH_4]_2{}^{1/2} &+ k_2[LiAlH_4]_2 \\ &+ k_3[LiAl(O\text{-}t\text{-}Bu)H_3] \end{aligned} \quad (7)$$

In practice, the PLATO IV computer-based teaching system[34] was used to solve eq 5 and 6 for the equilibrium concentrations of hydride species, using a Newton–Raphson method to extract the roots of the fourth-order polynomial derived from eq 5.[35] The equilibrium constants were adjusted to obtain a good fit to the kinetic data. Figure 6 is a plot of k_{rel} vs. [t-BuOH]:[$LiAlH_4$] for reduction of ketone **1a** at an initial $LiAlH_4$ (total aluminum) concentration of 0.0242 M and initial ketone concentration of 4.22×10^{-4} M, using the value for k_1 of 4.1 $M^{-1/2}$ s^{-1} obtained from previous kinetic measurements (Table I). An excellent fit to the data in Figure 6 is obtained using $K_1 = 2.75$ M^{-1} and $K_2 = 0.26$. That is, with this hindered ketone, the data are well represented by reaction occurring only through monomeric $LiAlH_4$.

These equilibrium constants appear to be a unique solution and agree with Kader's NMR studies of lithium *tert*-butoxyaluminohydrides.[18] In addition, Kader's observation of sharp signals for the resonances due to the *tert*-butyl protons suggests that the ligand exchange process is fast on the NMR time scale. The disproportionation model used in the present study assumes that equilibration of the alkoxyaluminohydrides occurs more rapidly than ketone reduction.

The *tert*-butoxide kinetic data for ketone **2** (Figure 7) define a curve differing from that obtained for **1a** (Figure 6) in two major respects. First, reactions at low [t-BuOH]:[$LiAlH_4$] ratios have a higher relative rate for the less hindered ketone. Second, the reaction rate decreases more slowly for **2** than for **1a** with increasing [t-BuOH]:[$LiAlH_4$] ratios. The alkoxide kinetics for ketone **3** exhibit the same characteristics as do those of **2**, but these two alterations in the shape of the curve are even more pronounced with **3**.

The great difference in absolute reactivity among ketones **1a**, **2**, and **3** (Table IV) in reactions with $LiAlH_4$ can be attributed to the decreasing steric hindrance about the carbonyl group in the sequence **1a** > **2** > **3**. Similarly, the enhanced *relative* rate levels at low [t-BuOH]:[$LiAlH_4$] ratios for the alkoxide reductions of ketones **2** and **3**, compared with **1a**, suggest that an additional reducing agent is contributing to the reduction process as the degree of steric hindrance about the carbonyl diminishes. This contribution has been attributed to the monoalkoxy species, $LiAl(O\text{-}t\text{-}Bu)H_3$, as these kinetic results do not require that more than one of the alkoxyaluminohydrides present be involved in the reduction of these ketones.

Accordingly, the alkoxide data for **2** and **3** were fit with eq 7, using the rate constants for monomeric and dimeric $LiAlH_4$ determined previously, and using the same values for K_1 and K_2 which were used to fit the alkoxide data from ketone **1a**. As seen in Figure 7, the data for ketone **2** are adequately described by using a value of 1100 M^{-1} s^{-1} for k_3. A similar treatment of the alkoxide data obtained for ketone **3** yielded a value of 9000 M^{-1} s^{-1} for k_3 (Figure 8).

A calculation of the percentage of total reduction proceeding via each species ($LiAlH_4$ monomer and dimer, and $LiAl(O\text{-}t\text{-}Bu)H_3$) at various molar ratios indicates that dimeric $LiAlH_4$ never accounts for more than ca. 10% of the reduction process at the concentrations used in the alkoxide studies. However, based on the assumptions on the nature of the species in solution imposed by lack of data, the rate contribution from $LiAl(O\text{-}t\text{-}Bu)H_3$ becomes increasingly important, and this species accounts for about 50% of the total reduction at molar ratios of 1.7 for ketone **2** and 1.5 for ketone **3**.

Although this disproportionation model accurately describes the alkoxide kinetics presented here, the assumptions regarding the state of aggregation of the *tert*-butoxides may be oversimplified. Experiments are being undertaken to examine the kinetics of lithium *tert*-butoxyaluminohydride reductions of ketone **1a** as a function of the total aluminum concentration. Such experiments may provide information regarding the actual states of aggregation of the various alkoxide species.

The kinetics of reduction of ketone **1a** by a series of reagents prepared by adding various quantities of **1a** to a stock solution of $LiAlH_4$ were also examined. While the same general features as observed in the *tert*-butoxide system are again present, suggesting that disproportionation is also taking place in this secondary alkoxide system,[15] the quantitative dependence of k_{rel} upon the molar ratio of alkoxide to $LiAlH_4$ is quite different from that seen in Figure 6. An acceptable fit to the data is obtained using $K_1 = 0.005$ M^{-1} and $K_2 = 15$.

These results suggest that the stereochemistry of lithium aluminohydride reductions of ketones may represent a composite effect, reflecting the stereoselectivities of all the effective reducing agents present in solution. The kinetics and stereochemistry of $LiAlH_4$ and lithium alkoxyaluminohydride reductions of some cyclic ketones are presently being investigated in an attempt to elucidate the factors governing the stereoselectivities of various hydride reducing agents.

Experimental Section

General. Ultraviolet spectra were recorded with a Perkin-Elmer Model 202 spectrophotometer using 1-cm quartz cells. Infrared spectra were obtained on a Perkin-Elmer Model 137B or Beckman IR-12 spectrophotometer in 1-mm NaCl cells. Nuclear magnetic resonance spectra were obtained on Varian T-60 and A-60A spectrometers and are reported in parts per million downfield from an internal Me_4Si standard. Analytical data were obtained by Mr. J. Nemeth and associates at the University of Illinois. Melting points were determined on a Büchi melting point apparatus in open capillaries and are uncorrected.

Kinetic Measurements and Data Analysis. All kinetic experiments were performed on a stopped-flow ultraviolet spectrophotometer which has been described previously.[28] Bath temperature was maintained at 25.0 ± 0.1 °C. The rate of disappearance of the ketone was followed at a wavelength between 250 and 290 nm and was wavelength independent for ketone **1a**. (Ketones **2** and **3** had to be studied above 260 nm due to interfering absorbances by the products.) Data were collected on a 32-channel analog input buffer, collecting points at intervals of 0.2 ms to 1 s. These data, together with the zero light level and infinity reading (taken after at least 10 half-lives), were then transferred to disk storage on the PLATO IV computer-based teaching system CDC Cyber 73 computer. Curves of percent transmittance vs. time were computer generated by connecting the 32 digitized light level measurements with straight line segments. All data were analyzed as pseudo first order in ketone. Standard first-order plots were typically linear over at least 5 half-lives, and rate constants were taken from unweighted least-squares analysis. Rate constants were generally reproducible to within ca. 3%. The rapid-scanning equipment has been described previously.[36]

Solutions. Solutions of lithium aluminum hydride were prepared in an all-glass, grease-free apparatus which was dried under vacuum and flamed dry prior to use and kept under positive pressure of argon gas (Linde, passed through 4 Å molecular sieves before use) during all operations. Reagent ether (Mallinckrodt) was freshly distilled from $LiAlH_4$ onto purified $LiAlH_4$. After stirring for 30 min and settling, the solution was filtered twice by argon pressure through sintered glass and delivered into silicone rubber serum-capped bottles. If desired, solutions were diluted directly in these bottles by addition of freshly distilled ($LiAlH_4$) ether. Ketone solutions were prepared by the distillation of dry ether into vacuum-dried bottles containing a weighed amount of ketone, and the volume of ether calculated from its weight.

Alkoxyaluminohydride Solutions. *tert*-Butyl alcohol was dried by passage through a 40-cm column packed with activated 4 Å molecular sieves, followed by distillation. Solutions of lithium *tert*-butoxyaluminohydrides were prepared by the addition via syringe of a weighed quantity of dry *tert*-butyl alcohol to a known volume of standardized $LiAlH_4$ solution. The resulting solutions were clear and colorless, although those solutions with a molar ratio of alcohol to $LiAlH_4$ of ca. 2.5 or greater did form a white precipitate after several minutes.

Reagent Analysis. The solutions of $LiAlH_4$ used in these studies were analyzed for total hydride by Felkin's iodine titration method.[37] A syringe aliquot of reagent was injected into a known excess of standard iodine in benzene. Water, dilute acetic acid, and ca. 5 ml of ethanol were added, and the excess iodine was back-titrated using standard aqueous sodium thiosulfate. The precision of duplicate analyses by this method is ca. 1%.

Purification of $LiAlH_4$.[38] Ether (100 ml) was distilled from $LiAlH_4$ under dry N_2 onto 7 g of commercial $LiAlH_4$ (Ventron). The resulting gray slurry was stirred for 2 days. After settling, the slurry was filtered on a sintered glass funnel in an argon-filled drybox, and the clear filtrate was concentrated by distillation to about 20 ml of syrupy solution. Benzene was dried by passage through a 40-cm column packed with activated Linde 4 Å molecular sieves and distilled under nitrogen into the concentrated ether solution of $LiAlH_4$ to a total volume of ca. 100 ml. The resulting white crystals of $LiAlH_4$ were filtered in the drybox on sintered glass, yielding about 5.5 g of purified material. Residual benzene was removed under vacuum. The kinetics of reduction of ketone **1a** using purified $LiAlH_4$ were within experimental error of those observed using commercial material; purified $LiAlH_4$ was used for all kinetic measurements.

Anal. Calcd for $LiAlH_4$: Al, 71.07; H, 10.64. Found: Al, 70.22; H, 10.75 (cf. analysis of commercial $LiAlH_4$: Found: Al, 62.81; H, 10.07).

2,4,6-Trimethylbenzophenone (1a). This compound was prepared by the method of Gore and Hoskins[39] and yielded 36.2 g (79%) of a liquid which crystallized upon standing for 6 months and was recrystallized from hexane (mp 34–35.5 °C) UV (ether) 221 nm (ϵ 9700), 247 (ϵ 14 600), shoulder at 280 (ϵ 2670); IR (film) 2930, 1675, 1615, 1448, 1315, 1270, 1173, 913, 854, 814, 748, 712 cm^{-1}; NMR (CCl_4) δ 2.05 (s, 6 H), 2.28 (s, 3 H), 6.80 (s, 2 H), 7.20–7.85 (m, 5 H).

Anal. ($C_{16}H_{16}O$) C, H.

2,4,6-Trimethylbenzhydrol. A solution containing **1a** (15.1 g, 0.067 mol) in 25 ml of ether was added dropwise with stirring to a suspension of $LiAlH_4$ (1.5 g, 0.04 mol) in 100 ml of ether under nitrogen. Excess $LiAlH_4$ was decomposed by the addition of 1.5 ml of H_2O, 1.5 ml of 15% NaOH, and 4.5 ml of H_2O. The mixture was filtered and the solid dissolved in 100 ml of 4 M H_2SO_4. The acid solution was extracted with ether, and the combined ether layers were washed with 10% $NaHCO_3$ and water and dried ($MgSO_4$). Removal of ether under reduced pressure and distillation at 154.5–157 °C (0.3 Torr) [lit.[40] 146 °C (0.8 Torr)] afforded 2,4,6-trimethylbenzhydrol (8.0 g, 53%) as a colorless, extremely viscous liquid: UV (ether) 233 nm (ϵ 2110), 256 (ϵ 450); IR (film) 3400, 2900, 1610, 1580, 1490, 1445, 1375, 1140, 1039, 1010, 890, 799, 718, 690 cm^{-1}; NMR (CCl_4) δ 2.14 (s, 6 H), 2.20 (s, 3 H), 2.69 (s, 1 H), 6.10 (s, 1 H), 6.69 (s, 2 H), 7.14 (s, 5 H).

2,2′-Diethylbenzhydrol. A Grignard reagent was prepared from magnesium turnings (5.0 g, 0.206 mol) and 2-ethylbromobenzene (25.0 g, 0.135 mol) in ether. After refluxing 45 min, a solution of ethyl formate (5.0 g, 0.0675 mol) in ether was added dropwise. The reaction mixture was stirred until it reached room temperature, then hydrolyzed with dilute sulfuric acid. The layers were separated, and the aqueous layer was extracted with ether. The ether layers were washed with 10% $NaHCO_3$ and with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to dryness under reduced pressure and the product recrystallized twice from hexane, yielding 7.6 g (47%) of 2,2′-diethylbenzhydrol: mp 69.5–71 °C (lit.[41] 66–68.5 °); UV (ether) 227 nm (ϵ 2375), 261 (ϵ 542); IR ($CHCl_3$) 3610, 3450 (broad), 3020, 2980, 2940, 1486, 1455, 1008, 611 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (t, J = 7.0 Hz, 6 H), 2.62 (q, J = 7.0 Hz, 4 H), 6.25 (s, 1 H), 7.22 (s, 8 H).

2,2′-Diethylbenzophenone (2). 2,2′-Diethylbenzhydrol (11.0 g, 0.0457 mol) was dissolved in 100 ml of reagent grade acetone and treated with 12.5 ml of a 2.7 M Jones reagent. After the usual workup,[42] the product was distilled at 105–106 °C (0.05 Torr) [lit.[41] 106–108 °C (0.3 Torr)], yielding 6.8 g (62%) of **2**: UV (ether) 218 nm (ϵ 7550), 248 (ϵ 10,750), shoulder at 280 (ϵ 2480); IR (film) 3075, 3025, 2980, 2940, 2880, 1671, 1601, 1578, 1457, 1300, 1263, 928, 760, 705 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 7.5 Hz, 6 H), 2.84 (q, J = 7.5 Hz, 4 H), 7.27 (m, 8 H).

Anal. ($C_{17}H_{18}O$) C, H.

2,2′-Dimethylbenzhydrol. A Grignard reagent was prepared as above from 6.1 g (0.25 mol) of magnesium turnings and 36.0 g (0.21 mol) of *o*-bromotoluene. A solution of 25.0 g (0.21 mol) of *o*-tolualdehyde in 50 ml of ether was added dropwise with stirring. Acidic hydrolysis yielded 32.0 g (73%) of crude product. After recrystallization from hexane, 2,2′-dimethylbenzhydrol (25.9 g, 59%) was obtained: mp 120–122 °C (lit.[43] 119 °C); IR (CCl_4) 3620, 3500 (broad), 3080, 3030, 2980, 1490, 1468, 1370, 1018, 618 cm^{-1}; NMR ($CDCl_3$) δ 2.08 (broad s, 1 H), 2.24 (s, 6 H), 6.09 (s, 1 H), 7.20 (m, 8 H).

2,2′-Dimethylbenzophenone (3). 2,2′-Dimethylbenzhydrol (22.8 g, 0.11 mol) was dissolved in 275 ml of reagent grade acetone and treated with 26.4 ml of a 2.7 M Jones reagent. After the usual workup,[42] 21.3 g (95%) of crude product was obtained. Two recrystallizations from hexane gave 18.6 g (83%) of **3** as fine white needles: mp 69.5–71 °C (lit.[43] 70–70.5 °C); UV (ether) 213 nm, 247 (ϵ 15 010), shoulder at 280 (ϵ 2750); IR (CCl_4) 3070, 3025, 2970, 1670, 1467, 1303, 1258, 925, 790, 644 cm^{-1}; NMR (CCl_4) 2.44 (s, 6 H), 7.20 (s, 8 H).

Anal. ($C_{15}H_{14}O$) C, H.

Preparation of Substituted 2,4,6-Trimethylbenzophenones. Ketones **1b–1h** were prepared by the Friedel-Crafts acylation of mesitylene (1.0 equiv) with the corresponding substituted benzoyl chloride (1.0 equiv) in the presence of anhydrous $AlCl_3$ (1.1 equiv) in 1,2-dichloroethane solvent. In the general procedure, $AlCl_3$ was added in small portions to the other reactants and the resulting dark red mixture stirred and warmed gently for 1 h. The reaction mixture was then poured onto crushed ice drenched with concentration hydrochloric acid and worked-up in the usual fashion. The products were recrystallized two–five times from methanol and/or hexane All compounds gave satisfactory analyses for carbon, hydrogen, and halogen (when present). The NMR spectra of the ketones were all consistent with the expected structures and did not indicate the presence of any impurities.

The acid chlorides used to prepare **1b–1f** were purchased from Aldrich Chemical Co. and were used as received. In the preparation of **1g** and **1h**, *m*- and *p*-bromobenzotrifluoride, respectively, were reacted with magnesium turnings to form the Grignard reagent, which was carbonated by pouring onto excess powdered dry ice. The purified carboxylic acids were then refluxed with excess thionyl chloride, followed by removal of excess thionyl chloride under reduced pressure and vacuum distillation of the acid chlorides.

Below are listed the melting points, literature melting points (in parentheses), and yields (after two recrystallizations) of ketones **1b–1h**:

2,4,6-Trimethyl-4′-methoxybenzophenone (1b), mp 76.5–78.2 °C (77–78 °C[44]); 49%. **2,4,4′,6-Tetramethylbenzophenone (1c)**, mp 39–41 °C (32–33 °C[44]); 45%. **2,4,6-Trimethyl-4′-chlorobenzophenone (1d)**, mp 67–69 °C; 63%. **2,4,6-Trimethyl-4′-bromobenzophenone (1e)**, mp 71-72 °C (70–72 °C[44]); 67%. **2,4,6-Trimethyl-3′-chlorobenzophenone (1f)**, mp 85–87 °C (85.4–86.0 °C[45]); 69%. **2,4,6-Trimethyl-3′-trifluoromethylbenzophenone (1g)**, mp 68–71 °C; 46%. **2,4,6-Trimethyl-4′-trifluoromethylbenzophenone (1h)**, mp 79–81 °C (79–81 °C[44]); 45%.

Product Studies. The reduction products of ketones **1a**, **2**, and **3** were determined in the following manner. A slurry of 0.1 g (2.6 mmol) of $LiAlH_4$ in about 25 ml of dry ether was prepared and stirred at room temperature for 10 min. A solution containing ca. 0.5 g of the ketone in 20 ml of ether was added dropwise and the mixture stirred for 10 min. The excess $LiAlH_4$ was decomposed by the cautious addition of water, followed by enough dilute sulfuric acid to dissolve the salts formed. The layers were separated, and the aqueous layer was extracted twice with ether. The combined ether extracts were washed with 10% $NaHCO_3$ and with water, then dried over $MgSO_4$, and filtered. After removal of ether on a rotary evaporator, the product was weighed and analyzed by NMR and by melting point determinations for solids. In each case the NMR spectrum showed only those signals due to the expected product. The following results were obtained:

2,4,6-Trimethylbenzophenone: 497 mg of ketone used, 469 mg of alcohol obtained (93.4%). 2,2′-Diethylbenzophenone: 500 mg of ketone used, 510 mg of alcohol obtained (101%); mp 71–73 °C. 2,2′-Dimethylbenzophenone: 482 mg of ketone used, 463 mg of alcohol obtained (95.2%); mp 121.5–122.5 °C.

Reduction of 2,4,6-Trimethylbenzophenone with $LiAlD_4$ in Ether. A slurry was prepared as above from 0.1 g of $LiAlD_4$ (Ventron) and 25 ml of dry ether. After addition of 435 mg of 2,4,6-trimethylbenzophenone and work-up as above, 416 mg (94.4%) of product was obtained. The NMR spectrum of the product was identical with that of authentic 2,4,6-trimethylbenzhydrol, except that the signal at δ 6.28 (methine proton) was absent.

Acknowledgment. This work was supported by National Science Foundation Grant MPS-73-08778. One of us

(K.E.W.) gratefully acknowledges receipt of a University of Illinois Fellowship (1976–1977).

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Synthesis of 1,4-Diketones by Oxidative Coupling of Ketone Enolates with $CuCl_2$

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Received June 14, 1976

Abstract: A full scope of oxidative coupling of lithium enolates providing a general and efficient preparation of 1,4-diketones was examined. The oxidative coupling of lithium enolates was performed by treating ketone enolates, which were prepared from ketone and lithium diisopropylamide in THF at −78 °C, with $CuCl_2$ in DMF. The use of DMF cosolvent was very crucial in the copper promoted oxidative coupling of lithium enolates. Methyl ketones ($RCOCH_3$) were oxidatively dimerized to 1,4-diketones ($RCOCH_2CH_2COR$) in excellent to moderate yields; but, increasing alkyl substitution at the coupling site resulted in a remarkable reduction in the yield of 1,4-diketone. Cross coupling of two different methyl ketones (CH_3COR and CH_3COR'), in which a threefold excess of one ketone enolate over another is used, led to the formation of a specific unsymmetrical 1,4-diketone ($RCOCH_2CH_2COR'$) in a satisfactory yield and selectivity. *cis*-Jasmone (**22**) and allyl rethrone (**23**) were synthesized by a new route via the oxidative cross coupling of acetone with (*Z*)-5-octen-2-one and of acetone with 5-hexen-2-one, respectively. Intramolecular coupling of diketone dienolates was also examined. Diketone dienolate of 1,1′-diacetylferrocene was oxidatively cyclized to give α,α'-dioxotetramethyleneferrocene (**24**) in 55% yield, while diketone dienolate of 1,2-dipivaroylethane underwent dehydrogenation to give (*E*)-1,2-dipivaroylethylene (**27**) in 75% yield. Finally, the oxidative coupling of some vinylogs of methyl ketones and acetates such as (*E*)-2,2-dimethyl-4-hexen-3-one (**29**) and (*E*)-ethyl crotonate (**32**) was investigated. Lithium enolates of vinylogs of methyl ketones and acetates were generated in situ at −78 °C by treating vinylogs of methyl ketones and acetates with lithium diisopropylamide in a mixed solvent of THF and HMPA. It is noteworthy that the oxidative coupling of enolates of vinylogs of methyl ketones and acetates produced γ,γ-coupling dimers and α,γ-coupling dimers prominently. α,α-Coupling dimer was produced only in a trace amount. This finding is in remarkable contrast with the fact that the enolates of vinylogs of methyl ketones and acetates undergo the nucleophilic reaction (alkylation and protolysis) at the α carbon exclusively.

A variety of synthetic methods for the preparation of 1,4-diketones have been developed, since 1,4-diketones are versatile intermediates for syntheses of some natural products and related compounds consisting of cyclopentenone[1] and furan[2] ring systems. One of the representative and attractive routes to 1,4-diketones involves the conjugate addition of acyl anion equivalents, such as nitro-stabilized carbanion,[3] lithium di[bis(phenylthio)methyl]copper,[4] and acyl carbonylnickelate,[5] to enones. Many other synthetic routes to 1,4-diketones have been reported.[6]

Transition metal promoted dimerization of carbanions has constituted a convenient method for the carbon–carbon bond formation in organic synthesis. Copper-promoted dimerizations of carbanions, which are stabilized by sulfonyl,[7] phos-