Reactions of Et_3ZnLi with Ketones: Electronic and Steric Effects[1]

Curtis A. Musser and Herman G. Richey, Jr.*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania l6802

hgr@chem.psu.edu

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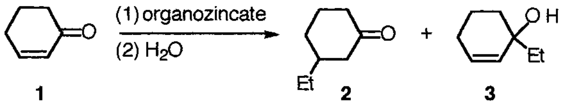
Toluene solutions of composition Et_3ZnLi react rapidly with aldehydes and ketones to form addition products. Et_3ZnNa and Et_3ZnK solutions react readily with the same substrates although metalation, as well as addition, is significant with substrates having α-hydrogens. The Et_3ZnM solutions react with 2-cyclohexenone to give mainly the 1,4-addition product. Relative rates of addition of Et_3ZnLi to substituted acetophenones give a Hammett ρ of 2.78. Addition of Et_3ZnLi to acetophenone is slowed significantly by α and ortho methyl substituents; relative rates of addition to acetophenone, *o*-methylacetophenone, and *tert*-butyl phenyl ketone are 1.00, 0.012, and 0.003.

Nearly 50 years ago Wittig and Lange reported that a solution of composition Ph_3ZnLi metalated fluorene, added to benzophenone, and added slowly to $PhCH{=}CHC({=}O)Ph$ to give 1,2- and 1,4-addition products; Ph_2Zn did not significantly undergo these reactions.[2] Solutions of composition R_3ZnLi have since been found to give other reactions not important for R_2Zn or RZnX, including metal−halogen exchange with 1,1-dibromoalkenes,[3] aryl iodides,[4] and 1,1-dibromocyclopropanes.[5] Most R_2Zn and RZnX compounds react sluggishly with aldehydes and not at all with ketones.[6] Addition to R_2Zn compounds of Bu_4NX salts somewhat increases the rate of reaction with benzaldehyde (and decreases the portion of reduction product),[7] and addition of *t*-BuOK permits addition to CO;[8] we now believe that these solutions contain organozincate species.[9] Organozincates (particularly of composition R_3ZnLi or R_3ZnMgX) react with α,β-unsaturated ketones, predominantly by 1,4-addition.[10] We set out to study reactions of organozincates with aldehydes and ketones.

Reactions of Organozincate Solutions with Aldehydes and Ketones. We found that several organozincate solutions react with aldehydes and ketones (eqs 1 and 2). Table 1 summarizes the results of adding carbonyl compounds to toluene solutions of organozincates at ambient temperature. Et_3ZnLi was prepared from Et_2Zn and EtLi,[11] Et_3ZnNa and Et_3ZnK were prepared from Et_2Zn and Na or K using procedures *described in l858*,[12] and $Et_2Zn(t\text{-}BuOK)$, $Et_2Zn(t\text{-}BuOLi)$, and $Et_2Zn(Bu_4NBr)$ were prepared from Et_2Zn and a salt. These formulas are compositions of the solutions and *imply neither molecular weights nor structures* of the dominant species.



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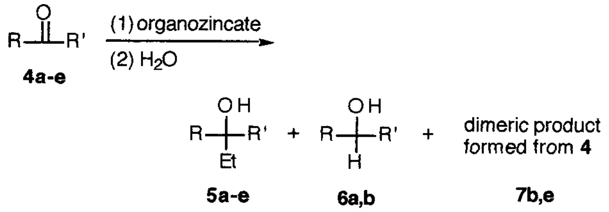

(2)

a: R = Ph R' = H
b: R = $CH_3(CH_2)_5$ R' = H
c: R = Ph R' = CH_3
d: R = Ph R' = Ph
e: R = CH_3 R' = $CH_2CH_2CH(CH_3)_2$

Et_2Zn, as expected, did not react significantly with any of the substrates in the indicated reaction times.[13] Benzophenone and Et_2Zn in refluxing toluene were reported to react but only to form reduction product **6d**; no reaction was observed with Me_2Zn.[14] By contrast, we found rapid reactions with several of the organozincate solutions, and a reduction product (**6**) never was significant. Et_3ZnLi gave good yields of addition product with all substrates, the 1,4-addition product **2** predominating from **1**. Reactions of Et_3ZnNa and Et_3ZnK with **1** also gave good yields

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[1] Much of this work is taken from Musser, C. A. Ph.D. Dissertation, The Pennsylvania State University, l994.

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[3] Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4897.

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[8] Rathke, M. W.; Yu, H. *J. Org. Chem.* **1972**, *37*, 1732.

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[10] Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, l991; Vol. 1 (Schreiber, S. L., Ed.), Section 1.7.3.2. Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: Boca Raton, l996; Chapter 4.

[11] Schlenk, R.; Holtz, J. *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 262. A Et_2Zn/EtLi ratio of 1.05 was used in our work reported in this paper. It is unlikely therefore that tetraethylzincate was present [Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934].

[12] Wanklyn, J. A. *Proc. R. Soc. London* **1858**, 341. Wanklyn, J. A. *Justus Liebigs Ann. Chem.* **1858**, *108*, 67.

[13] Benzaldehyde and Pr_2Zn in diethyl ether (not the toluene of this work) at 25 °C were reported to react slowly to give approximately equal amounts of an addition product and **6a**.[7]

[14] Coates, G. E.; Ridley, D. *J. Chem. Soc. (A)* **1966**, 1064.

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Table 1. Products from Reactions of Organozinc Reagents with Aldehydes and Ketones[a]

reactant	product	Et_2Zn[b] %	Et_3ZnLi[c] %	Et_3ZnNa[c] %	Et_3ZnK[c] %	$Et_2Zn(t\text{-}BuOLi)$[d] %	$Et_2Zn(t\text{-}BuOK)$[d] %	$Et_2Zn(Bu_4NBr)$[e] %
1	**1**	97	–	–	–	45	20	90
	2	–	98	87	97	2	40	2
	3	–	–	3[22]	–	1	–	–
4a	**4a**	98	–	–	–	59	3	61
	5a	–	97	97	87	34	94	38
	6a	–	2	2	12	6	–	–
4b	**4b**	98	–	4	3	36	60	96
	5b	–	95	90	85	–	–	–
	6b	–	2	2	2	9	–	1
	7b	–	–	3	9	33	20	–
4c	**4c**	99	–	27	62	97	100	99
	5c	–	98	71	36	–	–	–
4d	**4d**	101	–	–	–	99	–	98
	5d	–	99	97	99	–	101	–
4e	**4e**	98	3	38	38	55	49	98
	5e	–	94	37	31	–	–	–
	7e	–	–	23	28	40	50	–

[a] All reactions were at ambient temperature. [b] Reaction time was 24 h. [c] Reaction time was 10 min. [d] Reaction time was 15 min. [e] Reaction time was 1 h.

of **2**.[15] Starting material was recovered from reactions of Et_3ZnNa and Et_3ZnK with **4b**, **4c**, and **4e**, however, and the reactions with **4b** and **4e** each gave an additional product that was indicated by GC and MS data to result from aldol dimerization of the substrate. Some reactions of Et_3ZnNa and Et_3ZnK with these α-hydrogen-containing substrates were quenched with D_2O; MS analysis showed the recovered reactants to be mainly monodeuterated. Deuterium incorporation and dimer formation indicate significant metalation by Et_3ZnNa and Et_3ZnK. Reactions of solutions prepared from Et_2Zn and *t*-BuOK with **4b**, **4c**, and **4e** gave only recovered reactant and dimer; D_2O quenching indicated that the recovered reactants were mainly monodeuterated. The solutions prepared from Et_2Zn and *t*-BuOLi gave significant addition product only with benzaldehyde, but dimeric products and monodeuteration of recovered reactant indicated that metalation of **4c** and **4e** took place. Much lower yields of products were observed with solutions prepared from Et_2Zn and Bu_4NBr, and a D_2O quenching experiment showed no significant excess deuterium in recovered **4c**.[16]

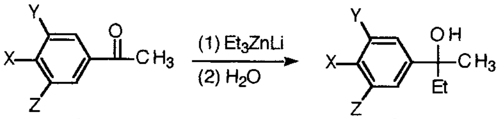
Electronic and Steric Effects on Additions of Et_3ZnLi to Acetophenones. On the basis of the results in Table 1, Et_3ZnLi was chosen for a study of structural effects on addition rate. Reactions with benzaldehydes and acetophenones at ambient temperature were complete within 30 s, about the shortest time in which reagents could be mixed and a sample taken, and therefore were too fast to study by quenching and analyzing aliquots. The half-time of a reaction of Et_3ZnLi (0.5 M) even with a dialkyl ketone, **4e** (0.02 M), was much less than 1 min.

Table 2. Relative Rates of Addition to SubstitutedAcetophenones and σ Values of Substituents

substituent	σ[19]	relative rate
$3,5\text{-}(CF_3)_2$	0.86[a]	34.8
4-CN	0.66	62.5
$4\text{-}CF_3$	0.54	13.8
$3\text{-}CF_3$	0.43	13.8
$3\text{-}C(=O)CH_3$	0.38	9.65[b]
3-Cl	0.37	6.17
3-F	0.34	5.01
4-Cl	0.23	2.61
$3\text{-}OCH_3$	0.12	1.03
4-F	0.06	0.82
none	0	(1.00)
4-Et	−0.15	0.38
$4\text{-}OCH_3$	−0.27	0.093

[a] Twice the $3\text{-}CF_3$ value. [b] One-half of the observed relative rate.

We decided therefore to determine *relative* rates using a competition procedure: the product composition when Et_3ZnLi is added to an excess of a pair of ketones could give the relative reactivities of those ketones. Addition of a toluene solution of Et_3ZnLi to toluene solutions of the acetophenones **8** in Table 2 (eq 3) led to >98% formation of addition products **9** except with **8c** and **8i**, each of which formed a small amount (<5%) of a second product.[17] Nitro-substituted acetophenones gave complex product mixtures and hence were not used. Reactions usually were quenched after 1 min, although reaction



(3)

8a-m **9a-m**

a:	X = H	Y = H	Z = H
b:	X = F	Y = H	Z = H
c:	X = Cl	Y = H	Z = H
d:	X = Et	Y = H	Z = H
e:	$X = CF_3$	Y = H	Z = H
f:	X = CN	Y = H	Z = H
g:	X = OMe	Y = H	Z = H
h:	X = H	Y = F	Z = H
i:	X = H	Y = Cl	Z = H
j:	X = H	$Y = CF_3$	Z = H
k:	X = H	Y = C(=O)Me	Z = H
l:	X = H	Y = OMe	Z = H
m:	X = H	$Y = CF_3$	$Z = CF_3$

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[15] A minor product (ca. 5−10%) in the reaction of Et_3ZnNa and **1** probably was a 1,3-diethylcyclohexanol isomer [Richey, H. G., Jr.; Farkas, J., Jr. *Organometallics* **1990**, *9*, 1778].

[16] Addition of a diethyl ether solution of $Pr_2Zn(Bu_4NBr)$ to benzaldehyde has been reported to be four times faster than addition of Pr_2Zn.[7]

[17] The minor product, more volatile than the starting material and apparently different for the two chloroacetophenones, was not acetophenone or *m*- or *p*-ethylacetophenone.

times of 10 min did not change yields or product compositions (for the **8a**–**e** pair, reaction times even of several hours gave the same product compositions). A study of yields (particularly with **8a**, **8e**, and **1**) indicated that only one-third of the ethyl groups of a Et_3ZnLi solution were incorporated into addition products.

Initial experiments with pairs of acetophenones suggested that substituent effects are small, but the results were not reproducible. We suspected that the ketones seemed deceptively similar in reactivity because addition was more rapid than the mixing that ideally would ensure that Et_3ZnLi always encounters a constant ratio of the two ketones. Reproducible results finally were obtained by using a lower temperature and very slow addition of Et_3ZnLi to the solution of ketones. The extent to which the temperature could be lowered was limited by decreasing solubility of some acetophenones; −41 °C finally was selected, although *m*-cyano-, *p*-(*N*,*N*-dimethylamino)-, and *p*-acetylacetophenone had to be eliminated from the study because their solubilities were too low at that temperature. A syringe pump was used to add the Et_3ZnLi solution; the needle through which addition was made was placed below the surface of the stirred solution of ketones so that addition was continual rather than in drops. To ensure that the mixing rate no longer affected the results, a series of competition reactions were run using **8a** and **8e**. Since **8e** was one of the most reactive substrates, effects of incomplete mixing should be noticeable with this reactant pair. The addition rate was decreased until the product ratio did not change; an even slower rate was used for the competition experiments.

Most ketones were compared directly with acetophenone (**8a**). Since the reactions used 10 mol of each acetophenone for each mole of Et_3ZnLi, the ratio of ketones did not change greatly over the course of a reaction. When one of the pair of ketones was significantly more reactive than the other, however, an adjustment was made for depletion.[18] The rates of **8f** and **8m**, very much greater than that of **8a**, were measured against **8e**. To compare **8k** and the much less reactive **8a**, a 6:14:1 (**8k**:**8a**:Et_3ZnLi) reactant composition was used. The relative reactivity values could be checked by comparisons other than those reported in Table 2. For example, the data in the Table indicate that **8e** is 2.24 times more reactive than **8i**; an experiment using these ketones gave a ratio of 2.40. Similar comparisons (from Table 2, from direct comparison) were made for **8e** and **8c** (5.29, 6.66), **8e** and **8k** (1.43, 1.26), and **8d** and **8g** (4.09, 3.93).

A plot of log(relative rate) versus Hammett σ values[19] is shown in Figure 1. The relative rate of the *m*-acetyl compound (**8k**) was halved because of its two equivalent reactive sites. We could not find a value for $3,5\text{-}(CF_3)_2$ substitution and so doubled the value for a $3\text{-}CF_3$ substituent. The largest deviation in the plot was for the $3,5\text{-}(CF_3)_2$ compound (**8m**); since a reliable σ value was not available, this point was not used in determining the slope, $\rho = 2.78$ ($r^2 = 0.973$), of the line that best fits the data. A plot using σ^- values[19] was much poorer ($\rho = 2.13$, $r^2 = 0.932$).

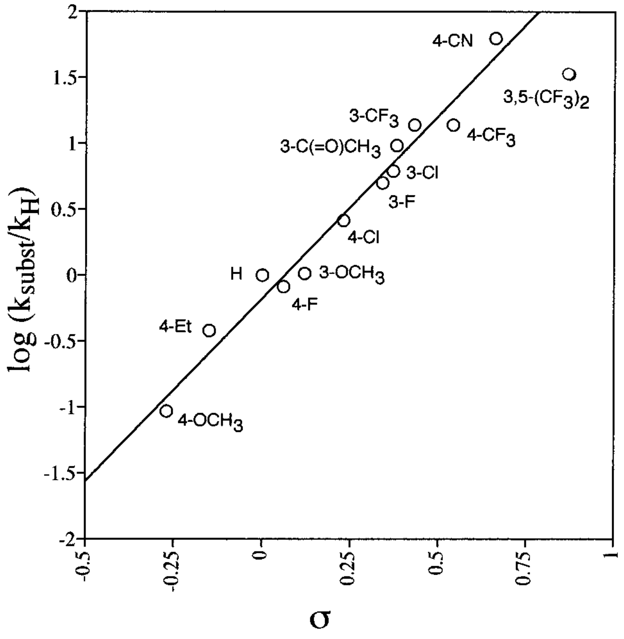
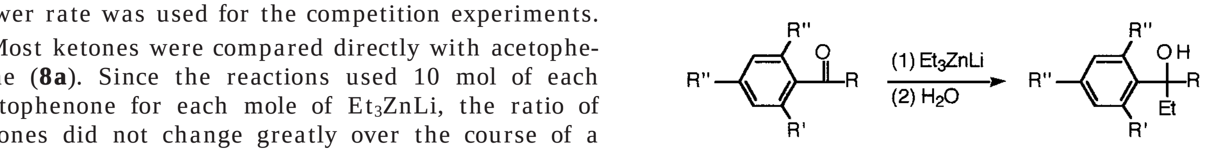


Figure 1. Hammett plot of relative rates of addition at −41 °C of a toluene Et_3ZnLi solution to acetophenones. The ρ (omitting the $3,5\text{-}(CF_3)_2$ compound) is 2.78.

Steric effects were probed by studying reactions of Et_3ZnLi with a group of acetophenones (**10a**–**f**) substituted with α and ortho methyl groups (eq 4). Addition product **11** and 5–10% of recovered reactant were found in reactions of **10b**, **10c**, and **10e**. Only reactant was isolated from reactions of **10f**, but it had been metalated since MS analysis, after quenching with D_2O, showed most of it to be monodeuterated. Reaction of **10d** gave both reduction (27%) and addition (70%) products.[20] The relative rates of additions to **10a**–**e**, benzophenone, and 2-cyclohexenone were determined by competition experiments. Values for **10b**, **10c**, **10e**, and benzophenone were determined by competition with acetophenone (**10a**). The same value for the relative rate of **10e** was obtained in a competition experiment with **8g** (whose rate relative to acetophenone was known). The relative rates of **10d** and 2-cyclohexenone, the least and most reactive of this group of substrates, were determined by competition with **10e** and **8e**, respectively.



(4)

10a-f **11a-f**

a:	R = Me	R' = H	R'' = H
b:	R = Et	R' = H	R'' = H
c:	R = *i*-Pr	R' = H	R'' = H
d:	R = *t*-Bu	R' = H	R'' = H
e:	R = Me	R' = Me	R'' = H
f:	R = Me	R' = Me	R'' = Me

The relative rates for methyl, ethyl, isopropyl, *tert*-butyl compounds **10a**–**d** were 1.0, 0.28, 0.099, and 0.003; the relative rate of *o*-methyl compound **10e** was 0.012.

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[18] For ketones A and B, A considerably more reactive than B, the relative rate ratio (k_A/k_B) was determined as $([B]_0/[P]_t)\ln([A]_0/[A]_t)$ where P is the product formed from B. The adjustments were small, the effect on rate ratio never exceeding 7%.

[19] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

[20] Et_3ZnNa and **10d** also gave reduction (19%) and addition (79%) products.

Table 3. Effect of Added TMEDA on NMR Spectra of Et_3ZnLi[a]

solution	^{1}H NMR, δ				^{13}C NMR, δ			
	$\mathrm{CH_3C}\mathit{H}_2\mathrm{M}$	$\mathrm{C}\mathit{H}_3\mathrm{CH_2M}$	CH_3N	CH_2N	$\mathrm{CH_3}\mathit{C}\mathrm{H_2M}$	$\mathit{C}\mathrm{H_3CH_2M}$	CH_2N	CH_3N
EtLi	−0.90	1.30						
Et_2Zn	0.11	1.10			6.7	10.3		
Et_3ZnLi	−0.23	1.33			2.0	12.1		
TMEDA			2.29	2.10			58.7	46.0
Et_3ZnLi/0.22 TMEDA	−0.11	1.46	1.46	1.60				
Et_3ZnLi/1.0 TMEDA	0.23	1.82	1.49	1.62	4.4	13.8	56.5	45.5
Et_3ZnLi/1.5 TMEDA	0.17	1.90	1.76	1.83	3.8	14.5	57.0	45.9
Et_3ZnLi/2.0 TMEDA	0.28	1.87	1.85	1.88				
Et_2Zn/1.0 TMEDA	0.21	1.73	1.99	2.05				
EtLi/1.1 TMEDA	−0.73	1.90	2.09	2.02				
Et_3ZnLi[b]	−0.27	1.20						
TMEDA[b]			2.36	2.20				
ET_3ZnLi/1.0 TMEDA[b]	−0.27	1.20	2.36	2.20	5.0	15.5	58.5	46.7
Et_2Zn/1.0 *t*-BuOLi	−0.08	1.10		1.24[c]	6.9	10.5	66.9[d]	35.7[e]

[a] The solvent is benzene-d_6 except where noted. [b] The solvent is THF-d_8. ^{1}H NMR absorptions are reported relative to internal $-OCHDCD_2-$ (δ 3.60) and ^{13}C NMR absorptions relative to internal $-\mathit{C}D_2CD_2O-$ (δ 26.50). [c] $\mathrm{C}\mathit{H}_3\mathrm{CO}$ absorption. [d] $\mathrm{CH_3}\mathit{C}\mathrm{O}$ absorption. [e] $\mathit{C}\mathrm{H_3CO}$ absorption.

The relative rates for benzophenone and 2-cyclohexenone (also relative to acetophenone) were 1.2 and 14, respectively.

Modification of the Organozincate Reagent. Absorptions from some of the NMR spectra of solutions prepared by adding TMEDA to benzene-d_6 solutions of Et_3ZnLi are given in Table 3. Until the TMEDA:Et_3ZnLi ratio reached 1, the ethyl absorptions shifted to higher frequency, and the TMEDA absorptions were characteristic of TMEDA coordinated to a metal. After the ratio exceeded 1, the positions of the TMEDA absorptions approximated weighted averages of those of free and coordinated TMEDA, and the ethyl absorptions underwent only small changes. When TMEDA was added to Et_3ZnLi in THF-d_8, however, the ^{1}H NMR absorptions of Et_3ZnLi and TMEDA were unchanged. These observations indicate that TMEDA is coordinated to a metal in benzene-d_6 solutions but not significantly in THF solutions. Addition of TMEDA conceivably might form EtLi + Et_2Zn(TMEDA) or EtLi(TMEDA) + Et_2Zn, but comparisons with NMR spectra of EtLi−TMEDA and Et_2Zn−TMEDA solutions show that the ethyl absorptions of the Et_3ZnLi−TMEDA solutions differ significantly from the weighted averages expected if EtLi(TMEDA) or Et_2Zn(TMEDA) formation was appreciable. TMEDA therefore interacts with the organozincate without converting large amounts of it to Et_2Zn and EtLi; moreover, the solutions containing TMEDA still gave principally 1,4-addition with **1** (**2**:**3** > 10), although alkyllithium compounds give principally 1,2-addition.[21]

Discussion

In contrast to Et_2Zn, Et_3ZnLi reacts rapidly with aldehydes and ketones to give good yields of addition products. Et_3ZnNa and Et_3ZnK also react rapidly, but metalation of substrates having α-hydrogens can be significant. Et_3ZnNa and Et_3ZnK give mainly 1,4-addition to α,β-unsaturated ketone **1**, as already well-known for Et_3ZnLi. Et_2Zn(*t*-BuOK) adds rapidly to the substrates without α-hydrogens, but metalation is the principal reaction with substrates having α-hydrogens. Et_2Zn(*t*-BuOLi) and $Et_2Zn(Bu_4NBr)$ form addition product only with benzaldehyde; the former metalates substrates having α-hydrogens, but the latter does not undergo even this reaction.

What organozinc species are responsible for the reactions? NMR studies[22] of benzene solutions of EtLi plus Et_2Zn indicate formation of a species having a 1:1 ratio of the reactants, and molecular weight determinations[23,24] indicate the composition to be $(EtLi)_2(Et_2Zn)_2$. NMR observations indicate that mixed species form even in coordinating solvents: 2:1 and 3:1 ($MeLi:Me_2Zn$) in diethyl ether[25] and 1:1 and 2:1 in THF.[26] X-ray crystal structural studies have found R_3Zn^- Li^+ structures in which Li^+ is coordinated with TMEDA[27,28] or 1,3,5-trimethylhexahydro-1,3,5-triazine,[28,29] and there is some NMR evidence for R_3Zn^- ions in solution.[30] The NMR results (Table 3) with Et_3ZnLi−TMEDA solutions indicate that TMEDA is coordinated to a metal (probably to Li, as in structures[27,28] mentioned above). Et_3ZnNa and Et_3ZnK in benzene also are dimeric,[23] but X-ray studies[31] show Np_3ZnNa, Np_3ZnK, and $(Me_3SiCH_2)_3ZnK$ solids to have essentially independent R_3Zn^- and Na^+ or K^+ ions.[32]

A species having a 1:1 ratio of the reactants is the principal component in solutions prepared from equimolar amounts of *t*-BuOK and an R_2Zn compound;[33,34] X-ray analysis[33] shows a Et_2ZnO-*t*-Bu^- K^+ dimer whose Zn atoms share two bridging *t*-BuO groups. We know of no observation concerning *t*-BuOLi−R_2Zn compositions ex-

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[21] A recent example of 1,2-addition of an alkyllithium compound: Rijnberg, E.; Jastrzebski, T. B. H.; Boersma, J.; Kooijman, H.; Veldman, N.; Spek, A. L.; van Koten, G. *Organometallics* **1997**, *16*, 2239.

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[26] Seitz, L. M.; Little, B. F. *J. Organomet. Chem.* **1969**, *18*, 227.

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[30] X-ray structures of the type $(Li^+)_2(R_4Zn)^{2-}$ also are known: Weiss, E.; Wolfrum, R. *Chem. Ber.* **1968**, *101*, 35 (1968). Fröhlich, H.-O.; Kosan, B.; Müller, B.; Hiller, W. *J. Organomet. Chem.* **1992**, *441*, 177. Fröhlich, H.-O.; Kosan, B.; Undeutsch, B.; Görls, H. *J. Organomet. Chem.* **1994**, *472*, 1.

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cept that in Table 3; the minimal changes in position of NMR absorptions of the Et groups when *t*-BuOLi is added to a Et_2Zn solution suggest that formation of a mixed species is insignificant. NMR studies of R_2Zn-Bu_4NBr solutions hint that mixed species form, but are inconclusive because changes of absorption positions are small.[34]

These observations suggest that organozincate species are major components in the Et_3ZnLi, Et_3ZnNa, Et_3ZnK, and $Et_2Zn(t\text{-}BuOK)$ solutions. Organozincates probably are responsible for the additions, a conclusion supported by the observations that only one-third of the ethyl groups of an Et_3ZnLi solution add to acetophenones or to 2-cyclohexenone. The additions cannot be due to Et_2Zn, itself unreactive with the substrates; at least in reactions with **1**, neither are they due to EtLi, since **3** would be the principal product.[21,35] The $Et_2Zn(t\text{-}BuOLi)$ and $Et_2Zn(Bu_4NBr)$ solutions are far less reactive, adding significantly only to benzaldehyde; any organozincates in these solutions must be less reactive or (as seems probable with the former) present in lesser amounts.

Mechanisms of Reactions of Et_3ZnLi Solutions with Acetophenones. The ρ of 2.78 found for reactions of Et_3ZnLi solutions and acetophenones is much larger than ρ values reported for most similar reactions of other polar organometallic reagents: 0.4−1.4 for seven additions[36−38] of methyl, butyl, and phenyl Grignard reagents to acetophenones or benzophenones and 0.2−0.3 for four additions[38−41] of methyllithium, butyllithium, and phenyllithium to benzaldehydes or benzophenones. The only comparable value, $\rho = 3.0$, is for additions of *t*-BuMgCl to benzophenones,[37] reactions in which electron transfer from the organometallic reactant to the ketone is generally thought to be rate-determining.[42,43]

The rate-decreasing effects of α and ortho methyl groups evident in additions to **10a**−**f** must be principally steric. A direct electronic effect of the only weakly electron-releasing methyl groups cannot account for the large rate differences (note the relatively small effect of the para ethyl group of **8d**). In fact, for the **10a**−**d** series, a plot of log(relative rate) against the Taft E_s parameter[44] gives a reasonable correlation ($\delta = 1.50$, $r^2 = 0.970$).[46,47] However, α and ortho methyl groups could have an indirect electronic consequence—by increasing the torsional angle[48] between the aryl ring and the carbonyl group, they diminish aryl−carbonyl conjugation in the acetophenone and in some possible intermediates. Could the effects of the methyl groups be due principally to making electron transfer more difficult by increasing the torsional angle? $E_{1/2}$ in an aprotic solvent is reported to be 0.16 V more negative for **10d** than for acetophenone,[49] a difference that must reflect the combined effects by the added methyl groups of increased torsional angle and weak electron release. The differences between **10d** and acetophenone in $E_{1/2}$ and in addition rate are of equivalent magnitude, consistent with an effect on electron-transfer rate being significant.[50] In the absence of more extensive studies of $E_{1/2}$ and an indication of error limits, however, this is only suggestive. Note that $E_{1/2}$ for benzophenone is reported[49] to be 0.16 V more positive than for acetophenone, but we found additions to these ketones to have almost identical rates.

Because of the large ρ, electron transfer seems probable in the reactions of Et_3ZnLi and acetophenones. Electron transfer can be susceptible to steric hindrance. In fact, Holm[42] proposed that electron transfer is rate-determining in some additions of organomagnesium compounds to ketones in which this step would be too endothermic to be significant unless the α-carbon of the Grignard reagent was partially bonded to the carbonyl carbon; the rate of electron transfer is significant only at those moments when the α-carbon and the carbonyl carbon are in close proximity, a proximity that is less frequent with increasing steric hindrance at the carbonyl carbon.

Experimental Section

^1H NMR absorptions are reported relative to internal C_5D_5H (δ 7.15) in benzene-d_6 solutions, internal $CHCl_3$ (δ 7.26) in $CDCl_3$ solutions, and internal $-CHDCD_2OCD_2CD_2-$ (δ 2.60) in THF-d_8 solutions; notations used are s, singlet; d, doublet; t, triplet; q, quartet; m, more complex multiplet; c, complex overlapping absorptions; br, broad. ^{13}C NMR absorptions are reported relative to internal C_6D_6 (δ 128.00) in benzene-d_6 solutions, internal $CDCl_3$ (δ 77.50) in $CDCl_3$ solutions, and internal $-\mathbf{C}D_2CD_2O-$ (δ 26.50) in THF-d_8 solutions. AAS analyses used an air−acetylene flame; concentrations were obtained from a calibration curve prepared from standard solutions.[51] Procedures involving organometallic compounds were performed under a nitrogen atmosphere using a vacuum line or a glovebox. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Benzene, toluene, and TMEDA were distilled from CaH_2; diethyl ether was distilled from sodium benzophenone ketyl; *t*-BuOLi and *t*-BuOK were sublimed.

Products. Some samples needed as GC standards for reaction products were obtained commercially. Several were synthesized by literature procedures: **2**,[15] **3**,[15] **5e**,[52] and 1,3-

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(35) It is conceivable that the organozincate species dissociates to form EtLi, which at that moment differs from and reacts in a different manner than $(EtLi)_6$, the dominant[23] species at equilibrium.

(36) Lewis, R. N.; Wright, J. R. *J. Am. Chem. Soc.* **1952**, *74*, 1257. Anteunis, M.; Van Schoote, J. *Bull. Soc. Chim. Belg.* **1963**, *72*, 776. Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* **1989**, *111*, 4912.

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(38) Yamataka, H.; Miyano, N.; Hanfusa, T. *J. Org. Chem.* **1991**, *56*, 2573.

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(40) Yamataka, H.; Kawafuji, Y.; Nagareda, K.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* **1989**, *54*, 4706.

(41) For reactions of benzophenones with methyllithium and ethyllithium, we have found somewhat larger ρ values (∼1): Maclin, K. M.; Musser, C. A. Unpublished work.

(42) For a recent review of mechanisms of additions of Grignard reagents, see Holm, T. In *Grignard Reagents: New Developments*; Richey, H. G., Jr., Ed.; Wiley: Chichester, 2000; Chapter 1.

(43) A relatively large ρ, 1.96, also is reported for addition of "Me_2CuLi" to benzophenones.[39]

(44) The values are taken from ref 45.

(45) Meyer, A. Y. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1567.

(46) The plot against V^n values[45] is less satisfactory ($\delta = -55.6$, $r^2 = 0.911$).

(47) The relative rates closely parallel those observed for reactions of the same substrates with PhMgBr: Van Schoote, J.; Anteunis, M. *Bull. Soc. Chim. Belg.* **1963**, *72*, 784.

(48) Barker, S. D.; Mirarchi, D.; Norris, R. K.; Phillips, L.; Ritchie, G. L. D. *J. Mol. Struct.* **1981**, *75*, 265, and references therein. Also see Andrieu, C. G.; Lumbroso, H. *Z. Naturforsch A* **1985**, *40*, 1329. Boykin, D. W.; Balakrishnan, P.; Baumstark, A. L. *Magn. Reson. Chem.* **1987**, *25*, 248.

(49) Saturated calomel electrode in DMF with Bu_4NI supporting electrolyte: Seguin, J.-P.; Beaupère, D.; Bauer, P.; Uzan, R. *Bull. Soc. Chim. Fr.* **1974**, 167.

(50) For polarographic data relating to these ketones in aqueous solutions and an introduction to problems in comparing measurements for different ketones, see Elving, P. J.; Leone, J. T. *J. Am. Chem. Soc.* **1958**, *80*, 1021.

(51) Skoog, D. A.; West, D. M. *Analytical Chemistry*, 3rd ed; Saunders: Philadelphia, l980; Chapter 17.

(52) Abbot, E. M.; Bellamy, A. J. *J. Chem. Soc., Perkin Trans. 2* **1978**, 254.

diethylcyclohexanol.[15] All others were obtained by routine additions of EtMgBr to an aldehyde or ketone. The following compounds apparently are new (NMR spectra in $CDCl_3$, ^1H at 300 MHz, ^{13}C NMR at 75 MHz).

2-(3-Acetylphenyl)-2-butanol: bp 108 °C (0.04 Torr); ^1H NMR 8.03 (dd, 1H, $J = 1.95, 1.82$ Hz), 7.81 (ddd, 1H, $J = 7.69, 1.82, 1.65$ Hz), 7.63 (ddd, 1H, $J = 7.84, 1.95, 1.82$ Hz), 7.42 (dd, 1H, $J = 7.84, 7.69$ Hz), 2.60 (s, 3H), 2.04 (br s, 1H), 1.85 (q, 1H, $J = 7.52$ Hz), 1.84 (q, 1H, $J = 7.36$ Hz), 1.56 (s, 3H), 0.78 (t, 3H, $J = 7.42$ Hz); ^{13}C NMR 198.48, 148.41, 136.92, 129.84, 128.31, 126.62, 124.66, 74.74, 36.64, 29.70, 26.69, 8.16. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.85; H, 8.50.

2-(4-Acetylphenyl)-2-butanol: bp 110 °C (0.035 Torr); ^1H NMR 7.92 (d, $J = 8.62$ Hz, 2H), 7.52 (dt, $J = 8.62, 1.94$ Hz, 2H), 2.59 (s, 3H), 1.91 (br s, 1H), 1.86 (q, $J = 7.49$ Hz, 1H), 1.84 (q, $J = 7.28$ Hz, 1H), 1.56 (s, 3H), 0.79 (t, $J = 7.44$ Hz, 3H); ^{13}C NMR 197.91, 153.19, 135.45, 128.25, 125.16, 74.94, 36.58, 29.75, 26.59, 8.11. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.87; H, 8.48.

2-(4-Cyanophenyl)-2-butanol: mp 55−56 °C (recrystallized from toluene after flash chromatrography[53]); ^1H NMR 7.63 (ddd, $J = 8.23, 2.12, 1.56$ Hz, 2H), 7.54 (ddd, $J = 8.23, 2.12, 1.56$ Hz, 2H), 1.84 (q, $J = 7.53$ Hz, 1H), 1.83 (q, $J = 7.36$ Hz, 1H), 1.72 (br s, 1H), 1.55 (s, 3H), 0.78 (t, $J = 7.43$ Hz, 3H); ^{13}C NMR 153.09, 131.98, 125.82, 118.98, 110.51, 74.82, 36.58, 29.76, 8.03. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.29; H, 7.46; N, 7.99.

2-(4-Ethylphenyl)-2-butanol: bp 70 °C (0.10 Torr); ^1H NMR 7.37 (d, $J = 8.1$ Hz, 2H), 7.19 (d, $J = 8.1$ Hz, 2H), 2.67 (q, $J = 7.6$ Hz, 2H), 1.85 (q, $J = 7.4$ Hz, 1H), 1.84 (q, $J = 7.3$ Hz, 1H), 1.82 (br s, 1H), 1.55 (s, 3H), 1.26 (t, $J = 7.6$ Hz, 3H), 0.83 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR 145.03, 142.30, 127.50, 125.39, 74.74, 36.58, 29.45, 28.30, 15.45, 8.32. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.96; H, 10.10.

2-(3-Methoxyphenyl)-2-butanol:[54] bp 86 °C (0.15 Torr); ^1H NMR 7.25 (dd, $J = 8.2, 7.7$ Hz, 1H), 7.03 (dd, $J = 2.1, 1.0$ Hz, 1H), 7.00 (ddd, $J = 7.7, 1.0, 1.0$ Hz, 1H), 6.78 (ddd, $J = 8.2, 2.1, 1.0$ Hz, 1H), 1.99 (br s, 1H), 3.81 (s, 3H), 1.83 (q, $J = 7.5$ Hz, 1H), 1.82 (q, $J = 7.2$ Hz, 1H), 1.53 (s, 3H), 0.81 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR 159.39, 149.60, 128.95, 117.28, 111.41, 111.02, 74.74, 55.05, 36.51, 29.51, 8.20. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.36; H, 8.86.

2-(2-Methylphenyl)-2-butanol: bp 45 °C (0.05 Torr); ^1H NMR 7.46 (dd, $J = 7.8, 2.0$ Hz, 1H), 7.21−7.16 (c, 3H), 2.59 (s, 3H), 2.06 (br s, 1H), 2.01 (q, $J = 7.4$ Hz, 1H), 1.97 (q, $J = 7.3$ Hz, 1H), 1.65 (s, 3H), 0.86 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR 144.55, 135.37, 132.42, 126.71, 126.65, 125.37, 76.01, 34.40, 28.69, 22.24, 8.51. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.30; H, 9.69.

Preparation of Et_3ZnLi Solutions. The preparation of EtLi solutions was adapted from a literature procedure.[11] Li powder (2 equiv) was added to a rapidly stirred toluene solution (1.0 M) of Et_2Hg. Unreacted Li powder floated on the surface until amalgamating with the Hg metal that was forming. Additional Li (0.2−0.3 equiv) was added after 24 h if unreacted Li was no longer evident. Additions of Li were repeated every 24 h until unreacted Li persisted. The mixture was filtered, and an aliquot of the resulting solution was hydrolyzed and titrated for base to provide the EtLi concentration. A portion of the EtLi solution was added to Et_2Zn (1.05 equiv), and the resulting Et_3ZnLi solution was diluted to 0.10 M by addition of toluene. The solutions were stable for several months, but eventually changed from colorless to yellow.

Preparations of Et_3ZnNa and Et_3ZnK Solutions. The preparations were adapted from literature procedures.[12,55] Small pieces of Na were added piece by piece to stirred Et_2Zn (4 equiv). There was an immediate exothermic reaction. The mixture was stirred for 12 h, resulting in a fine black powder suspended in a clear, colorless solution. Excess Et_2Zn was removed at reduced pressure leaving an oil and a black powder. Toluene was added to dissolve the oil, and the mixture was filtered through a fine fritted funnel. An aliquot of the filtered solution was hydrolyzed and titrated for base to determine the Et_3ZnNa concentration. Et_3ZnK was prepared and analyzed in a similar fashion except that much longer stirring times were required. AAS analysis of a typical solution found the Zn:K ratio to be 1.09. The Et_3ZnK could be crystallized from concentrated solutions and recrystallized from benzene or toluene. **On two occasions the crystalline material decomposed violently.** Toluene solutions of Et_3ZnNa and Et_3ZnK were initially clear and colorless, but precipitates formed within several days, presumably due to metalation of the solvent.

Preparations of Et_2Zn(*t*-BuOLi), Et_2Zn(*t*-BuOK), and $Et_2Zn(Bu_4NBr)$ Solutions. The salt (1 equiv) was added to a toluene solution of Et_2Zn. Et_2Zn(*t*-BuOLi) solutions were 0.10 M, and Et_2Zn(*t*-BuOK) and $Et_2Zn(Bu_4NBr)$ solutions were 0.20 M.

NMR Samples. NMR samples were prepared by removing solvent at reduced pressure from 1.0 mL of one of the above solutions (Et_3ZnLi was a viscous oil, Et_3ZnNa and Et_3ZnK were waxy solids). Then the deuterated solvent (1.0 mL) and any additives were added. The amount of added TMEDA was determined by NMR integrations.

Reactions of Organozincates with Aldehydes and Ketones (1 and 4a−e). A toluene solution of the carbonyl compound (1.0 mL, 0.15 M) and dodecane (ca. 0.03 M, known accurately in each case) as an internal standard was added dropwise to a stirred toluene solution of Et_2Zn (1.0 mL, 0.20 M) in a small conical vial that was maintained at 0 °C. The solutions were allowed to warm to ambient temperature and were stirred for 24 h. A piece of ice was added followed by a saturated aqueous NH_4Cl solution (1.5 mL) and diethyl ether (1.5 mL). The mixture was stirred briefly, the aqueous layer was removed from the bottom of the vial with a pipet, and $MgSO_4$ was added to dry the remaining liquid. The mixture was filtered through a piece of tissue (Kimwipe) that was lodged in a pipet and then analyzed by GC. The same procedure was used for reactions with the Et_3ZnM solutions except that (1) an appropriate volume of the Et_3ZnLi (0.1 M), Et_3ZnNa (0.32 M), or Et_3ZnK (0.1 M) solution was used to provide 0.2 mmol and (2) after addition was complete, the reaction solutions were removed from the ice bath and stirred at ambient temperature for only 10 min before hydrolysis. The procedure for the reactions with $Et_2Zn(Bu_4NBr)$, Et_2Zn(*t*-BuOLi), and Et_2Zn(*t*-BuOK) was the same as for the reactions with Et_3ZnM except that, after removal from the ice bath, the solution from the $Et_2Zn(Bu_4NBr)$ reaction was stirred at ambient temperature for 1 h before hydrolysis. White solids formed upon hydrolysis of the $Et_2Zn(Bu_4NBr)$ reactions, but GC analysis showed no significant (>2%) loss of products.

Competition Experiments. A solution of the two ketones (1.5 mL, 0.2 M in each) and dodecane (ca. 0.01 M, known accurately in each case) was prepared in a small conical vial and capped with a septum. The vial was removed from the glovebox, and the needle of a gastight syringe (Hamilton, 1.0 mL) containing a solution of Et_3ZnLi (0.30 mL, 0.10 M, 0.030 mmol) was inserted into the septum. The syringe was horizontal so that it could be placed in a syringe pump (Sage Instruments 341B), but the needle had been bent so that the portion inserted through the septum was vertical and reached below the surface of the solution of ketones. The vial was cooled (−41 °C) in an acetonitrile−liquid N_2 bath. The solution in the syringe was added over 8 min, and then the solution was allowed to stir briefly. Water (1.0 mL) was added, and the solution became cloudy. Dilute aqueous HCl was added dropwise with stirring until all solids disappeared. Control experiments showed that compositions did not change if solutions were stirred for much longer times after acid had been added.

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[54] Since this work was completed, alcohol **9l** has been noted in the literature, but without characterization or properties: Choi, J. H.; Youm, J. S.; Cho, C.-G.; Czae, M.-Z.; Hwang, B. K.; Kim, J. S. *Tetrahedron Lett.* **1998**, *39*, 4835.

[55] Hein, F.; Petzchner, E.; Wagler, K.; Segitz, F. A. *Z. Anorg. Allg. Chem.* **1924**, *141*, 161.

The aqueous layer was removed from the bottom of the vial with a pipet, and $MgSO_4$ was added to dry the remaining liquid. The mixture was filtered through a piece of tissue (Kimwipe) that was lodged in a pipet and then analyzed by GC. The reported results are the average of three experiments, and the range of values from individual experiments generally was $<\pm 2\%$. Additional experiments were done when the variation was larger.

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Supporting Information Available: GC conditions, retention times of products, response factors used for the products, and MS examination of products of reactions that were quenched with D_2O. This material is available free of charge via the Internet at http://www.pubs.acs.org.

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