in 2-butanone (3 ml) and treated with an excess of 1,5-cyclooctadiene to yield a crystalline olefin complex[17] (171 mg, 61%).

Kinetics of the Copper(I) Triflate Catalyzed Reaction of Ethyl Diazoacetate with Hexene-1. Apparatus. A 50-ml or 25-ml round-bottom flask with a long neck, which had a small side neck near the top with a 10/30 female joint, and a small side neck fitted with a rubber septum, was fitted with an outlet adapter which had a three-way stopcock, one of the arms of which was sealed with a rubber septum, another served as a vacuum takeoff. The flask was connected to a Dynisco APT85 pressure transducer which was equipped with a stainless steel male 10/30 joint. A B&F Instruments Model 1-110S transducer input conditioner was used to apply the voltage across the arms of a strain gauge and to direct the output signal to a Beckmann Model 1005 recorder (set for 10 mV full scale). The reaction temperature was maintained to ±0.2° with a mechanically stirred ethanol bath which was cooled with cold ethanol circulating through a 10 ft × 0.25 in. stainless steel coil. The circulating ethanol was cooled with a Neslab Instruments Model RTE-3 constant-temperature bath. The reaction mixture was magnetically stirred.

Reagent grade hexene-1 and hexane were purified by passage through a column of Activity I Woelm Basic alumina and degassed with a stream of dry nitrogen for 30 min. Ethyl diazoacetate was obtained from Aldrich Chemical Co. A standard solution of catalyst was prepared by dissolving $(CuOTf)_2$–C_6H_6 in hexene-1 under nitrogen.

Measurement Procedure. The reaction vessel was flushed with dry nitrogen and then charged with hexene-1 or a hexene-1–hexane mixture and either ethyl diazoacetate or an aliquot of catalyst solution. The reaction vessel was sealed and immersed in the cooling bath and then evacuated (to a pressure of 10–50 mm). Calibration was accomplished by the introduction of several 5-ml portions of dry nitrogen with a hypodermic syringe. The vessel was then re-evacuated and after 10–20 min of thermal equilibration either an aliquot of catalyst solution or ethyl diazoacetate was then added through the side neck with a Hamilton microliter syringe. Nitrogen evolution, which commenced immediately, was monitored electronically and recorded automatically. After cessation of nitrogen evolution, the reaction mixtures were washed and diluted with pentane and the resulting solution was washed with 10 ml of 2 *M* aqueous KCN. The organic solution was then concentrated by careful distillation of the solvent(s). Then ethyl phenylacetate was added as internal standard and the resulting mixture analyzed by vpc on a 10 ft × 1/8 in. 20% FFAP on 60–80 Chromosorb W (acid washed) column. Relative retention times on this column were: ethyl 2-butylcyclopropanecarboxylate, 0.41; diethyl fumarate, 0.67; diethyl maleate, 0.85; ethyl phenylacetate, 1.00; *cis*-triethyl cyclopropane-1,2,3-tricarboxylate,[35] 3.5; *trans*-triethyl cyclopropane-1,2,3-tricarboxylate,[35] 3.9. The various products and their yields obtained from the decomposition of ethyl diazoacetate in hexane solutions containing various concentrations of hexene-1 are listed in the Table V. Only *cis*-triethyl cyclopropane-1,2,3-tricarboxylate was formed and none of the trans isomer was detected. Its yield was, therefore, less than 1%. The observed strong preference for the formation of the cis isomer is reasonable, in view of the expected greater reactivity of maleate *vs.* fumarate and of the usual tendency of copper catalyzed cyclopropanations to favor the most sterically hindered product.

Table V. Variation of Product Yields with Concentration of Hexene-1 in Hexane

Hexene-1, *M*	Product yields (%)[a,b] A	B	C	D	Overall yield
0.8	48	7.6	3.8	3	62
1.8	59	4.3	2.3	3	69
3.2	65	2.5	1.5	2	71
4.8	74	2.0	1.1	2	79
8.0	75	1.4	0.8	2	79

[a] All products exhibited identical vpc retention times as those of authentic samples. In addition, the mass spectra of the products, separated from the mixtures by vpc, were identical with those of authentic samples. [b] A, ethyl 2-butylcyclopropanecarboxylate; B, diethyl fumarate; C, diethyl maleate; D, *cis*-triethyl cyclopropane-1,2,3-tricarboxylate.

Acknowledgment. We wish to thank the National Science Foundation for generous financial support of this research and Dr. S. F. Nelsen for his kindness in the loan of the apparatus for the measurement of gases.

Chemistry of Carbanions. XXIII. Use of Metal Complexes to Control the Aldol Condensation[1a]

Herbert O. House,* David S. Crumrine, Allan Y. Teranishi,[1b] and Hugh D. Olmstead[1c]

Contribution from the School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332. *Received August 28, 1972*

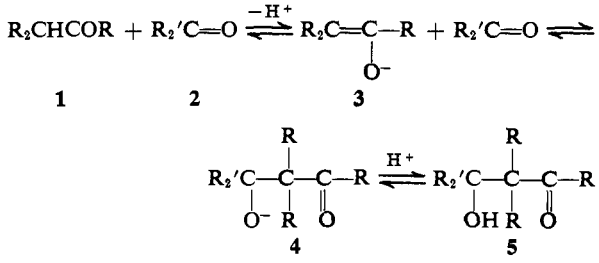
Abstract: Preformed lithium enolates may be used as reactants in aldol condensation with other carbonyl compounds provided reaction conditions are chosen that intercept the initially formed aldol products as metal chelates **9**. Although lithium may serve as the chelating metal cation in nonpolar solvents at low temperatures, it is experimentally more convenient to add a divalent metal salt such as anhydrous $MgBr_2$, or especially $ZnCl_2$. By adding an ethereal solution of $ZnCl_2$ to a preformed lithium enolate in ether or 1,2-dimethoxyethane solution, subsequent addition of either an aliphatic or an aromatic aldehyde results in the formation of a single aldol product in 80–90% yield. Where diastereoisomers of the aldol product are possible, there is usually a preference for the formation of the threo stereoisomer, the stereoisomer in which the greater number of substituents on the intermediate six-membered cyclic metal chelate may occupy equatorial conformations.

The aldol condensation (eq A)[2] has long presented organic chemists with the enigma of being a very rapid and efficient method for forming new carbon–carbon bonds and yet a reaction whose synthetic utility is severely curtailed in those instances where more

(1) (a) This research has been supported by Public Health Service Grant No. RO1-CA-12634 from the National Cancer Institute; (b) taken in part from the S.M. Thesis of A. Y. Teranishi, Massachusetts Institute of Technology, 1971; (c) taken in part from the Ph.D. Thesis of H. D. Olmstead, Massachusetts Institute of Technology, 1968.

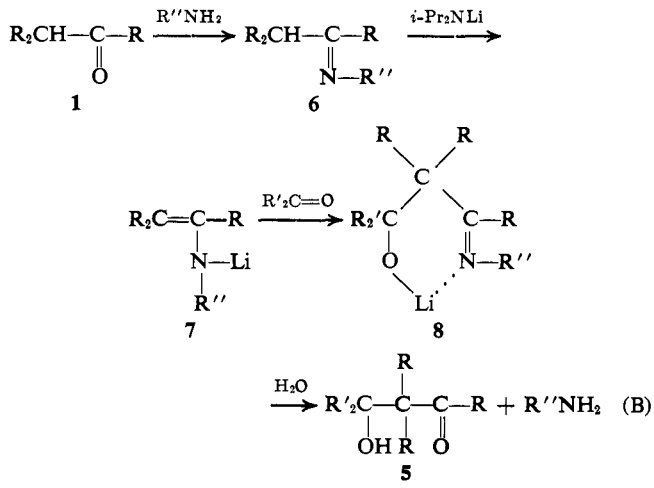
act., **16**, 1 (1968); (b) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Reading, Mass., 1972, pp 629–682.

(2) For reviews, see (a) A. T. Nielsen and W. J. Houlihan, *Org. Re-*



(A)

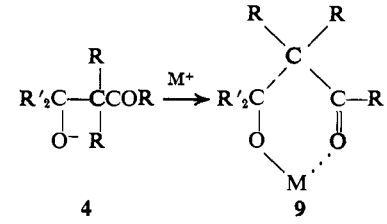
than one mode of condensation exists so that difficultly separable mixtures of aldol products result. Use of this reaction is often further complicated by the fact that the aldol product **5** is less stable than the starting materials **1** and **2**. Consequently, attempts to effect condensation under the equilibrium conditions implied in eq A will fail. Various methods to displace unfavorable equilibria such as dehydration of the aldol product **5** or its conversion to a β-chloro or β-acyloxy ketone have been successful only when certain rather restrictive structural features are present in the starting materials.[2] Apart from the common, but rather poorly understood, enzyme-catalyzed aldol condensations to form or break carbon–carbon bonds in biological systems, the most versatile of the synthetic procedures has been the directed aldol condensation procedure of Wittig.[3] In this method (see eq B) the



(B)

initial active methylene component is converted in stages to the lithio derivative **7** of the imine **6**. Addition of the lithio derivative **7** to a second carbonyl component is favored by the formation of the bidentate chelate **8** of the imino aldoxide in a nonpolar, aprotic solvent at low temperatures. The concept of displacing prior equilibria in favor of product formation was explicitly stated in the earlier formation of magnesium chelates of β-keto acid salts as a method for carboxylating active methylene compounds.[4]

It is apparent that this same principle of metal chelate formation could be used with the conventional aldol reactants (eq A) to intercept the intermediate keto alkoxide **4** as a metal chelate **9** (eq C). Provided the proper selection of metal cation and solvent is made such that the dissociation of the metal chelate is unfavorable, this method offers a procedure that



(C)

can both displace equilibria which would otherwise be unfavorable and can avoid common side reactions which plague typical aldol condensations such as di- and polycondensation and dehydration which may be followed by Michael addition of an enolate anion.[2] The best studied examples of this type of procedure have been the reactions of aldehydes or ketones with the bromozinc enolates of esters (the Reformatsky reaction)[2b,5] and ketones[6] in solvents such as benzene or ether. Halomagnesium enolates have been used in an analogous way,[2,7,8b,g] and even lithium enolates have been satisfactory when used at relatively low temperatures in ethereal solvents.[8]

With the present availability of several synthetic methods for the preparation of specific enolate anions (particularly lithium enolates) from unsymmetrical ketones[9] as well as aldehydes, esters, and nitriles it was appropriate to explore the use of specific metal enolates, prepared under nonequilibrating conditions, as reactants in the aldol condensation. In this study we have examined aldol reactions with the metal enolates (see Table I) **14**,[10] **19**, **25**, **36**, **48**, **49**, **54**, and **59** derived either from the ketones **10**–**12**, **33**, **46**, **53**, and **57** or from the enol acetates or enol silyl ethers **13**, **18**, **23**, **24**, **34**, **35**, **47**, and **55** (see Scheme I).

Selection and Application of Optimum Reaction Conditions. For our preliminary investigations we sought to avoid complex mixtures of reaction products by studying the aldol condensations of methyl ketones **10** and **11** and cyclohexanone (**33**) with benzaldehyde and of pinacolone (**12**) with both benzaldehyde and pivaldehyde. Although acetomesitylene (**10**) could be converted to the enol acetate **13** as an enolate precursor, a simpler route to the metal enolates **14** in this case in-

(3) (a) G. Wittig, *Rec. Chem. Progr.*, **28**, 45 (1967); (b) G. Wittig and A. Hesse, *Org. Syn.*, **50**, 66 (1970); (c) G. Wittig and H. Reiff, *Angew. Chem., Int. Ed. Engl.*, 7, 7 (1968).

(4) M. Stiles, *J. Amer. Chem. Soc.*, **81**, 2598 (1959); M. Stiles and H. L. Finkbeiner, *ibid.*, **81**, 505 (1959); **85**, 616 (1963).

(5) (a) R. L. Shriner, *Org. React.*, **1**, 1 (1942); (b) M. Mousseron, M. Mousseron-Canet, J. Neyrolles, and Y. Beziat, *Bull. Soc. Chim. Fr.*, 1483 (1963); (c) J. Canceill, J. J. Basselier, and J. Jacques, *ibid.*, 1024 (1967); (d) M. Bellassoued, R. Couffignal, and M. Gaudemar, *C. R. Acad. Sci., Ser. C*, 272, 1686 (1971), and earlier papers; (e) F. Lauria, V. Vecchietti, W. Logemann, G. Tosolini, and E. Dradi, *Tetrahedron*, **25**, 3989 (1969); (f) W. R. Vaughan, S. C. Berstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1790 (1965); W. R. Vaughan and H. P. Knoess, *ibid.*, **35**, 2394 (1970).

(6) T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Amer. Chem. Soc.*, **89**, 5727 (1967).

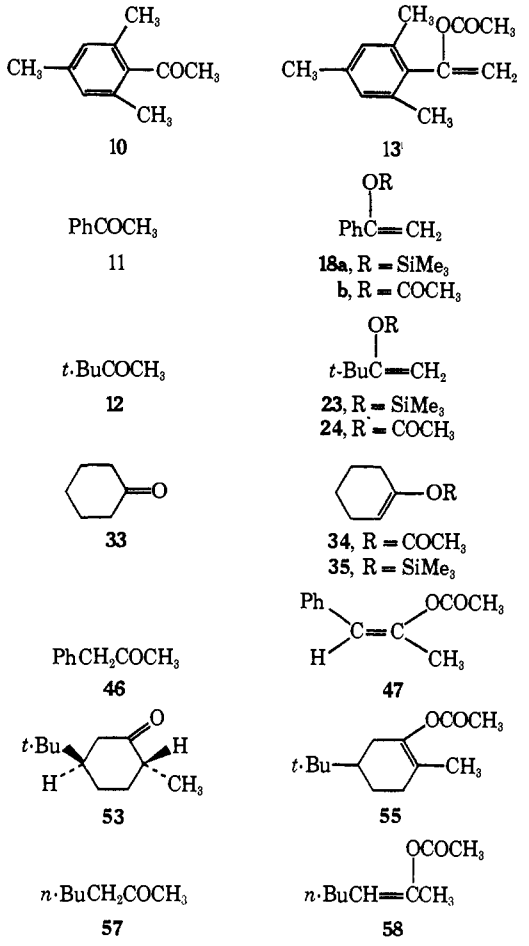
(7) For examples, see (a) A. T. Nielsen, C. Gibbons, and C. A. Zimmerman, *J. Amer. Chem. Soc.*, **73**, 4696 (1951); (b) H. E. Zimmerman and M. D. Traxler, *ibid.*, **79**, 1920 (1957); (c) T. Moriwake, *J. Org. Chem.*, **31**, 983 (1966); (d) J. A. Miller, M. H. Durand, and J. E. Dubois, *Tetrahedron Lett.*, **No. 32**, 2831 (1965); J. E. Dubois and J. Itzkowitch, *ibid.*, **No. 32**, 2839 (1965); (e) H. O. House, D. G. Melillo, and F. J. Sauter, *J. Org. Chem.*, **38**, 741 (1973).

(8) (a) C. R. Hauser and W. H. Puterbaugh, *J. Amer. Chem. Soc.*, **75**, 1068 (1953); (b) E. M. Kaiser and C. R. Hauser, *ibid.*, **89**, 4566 (1967); (c) M. W. Rathke, *ibid.*, **92**, 3222 (1970); (d) E. M. Kaiser, D. M. von Schriltz, and C. R. Hauser, *J. Org. Chem.*, **32**, 2610 (1967); **33**, 4275 (1968); (e) J. E. Dubois and M. Dubois, *Bull. Soc. Chim. Fr.*, 3120, 3553 (1969); (f) J. E. Dubois and J. F. Fort, *Tetrahedron*, **28**, 1653, 1665 (1972); (g) J. E. Dubois and P. Fellmann, *C. R. Acad. Sci., Ser. C*, **274**, 1307 (1972).

(9) For a recent summary with leading references, see H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).

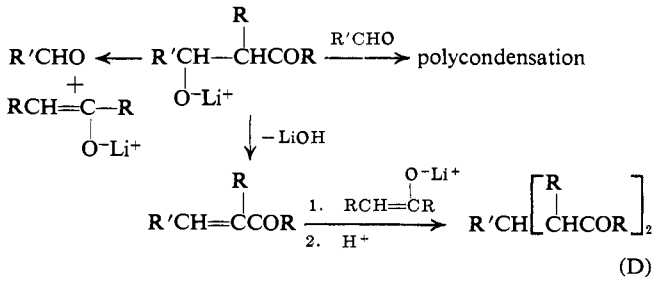
(10) For a study of the nmr spectrum of the bromomagnesium enolate (**14b**), see A. G. Pinkus, J. C. Lindberg, and A. B. Wu, *Chem. Commun.*, 1350 (1969); 859 (1970).

Scheme I



volved direct reaction of the hindered ketone **10** with methyllithium, dimethylmagnesium, or methylmagnesium bromide.[10] The lithium enolate **19** was obtained from the reaction of methyllithium with the corresponding silyl enol ether **18** and the lithium enolate **25** was obtained by each of the three previously developed methods,[9] reaction of the ketone **12** with the lithium diisopropylamide or reaction of methyllithium with either the silyl enol ether **23** or the enol acetate **24**. The same three methods were used with ketone **33**, enol acetate **34**, or silyl enol ether **35** to form the lithium enolate **36a**.

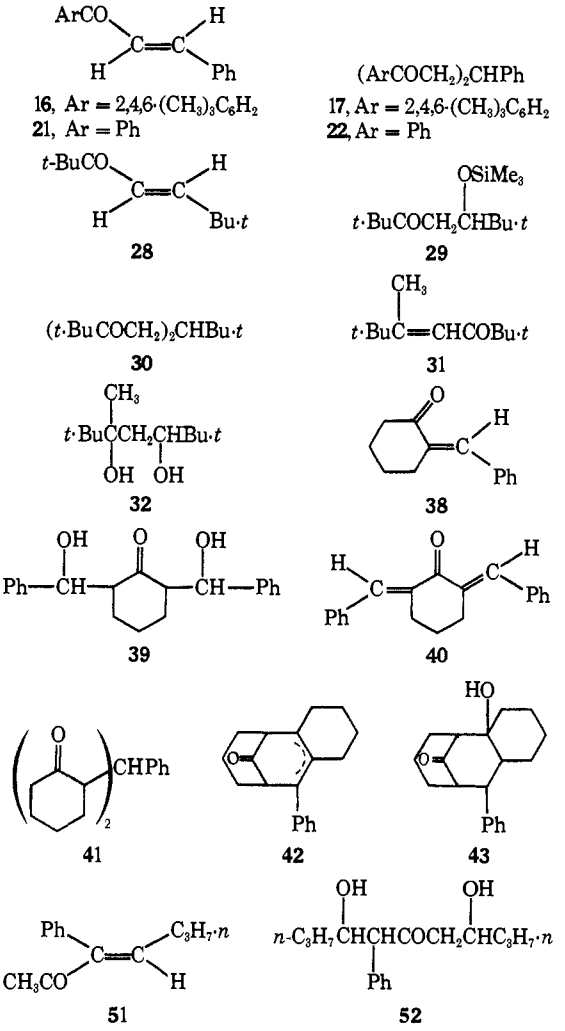
Initial studies with the lithium enolates **14a**, **25**, and **36a** (see Table I and Experimental Section, Tables II and III) in the absence of other metal cations established that satisfactory yields of aldol products could be obtained only at low temperatures (−20 to −50°) in ethereal solvents (Et_2O, THF, and DME). With only the lithium cation present, as the reaction temperature was raised to 0° or above the various side reactions (retrograde aldol, polycondensation, and enone formation followed by Michael addition) summarized in eq D became serious competitors. Consequently,



(D)

under conditions that did not favor the formation of a stable metal chelate **9** (see Experimental Section) various by-products such as **16**, **17**, **21**, **28**, **30**, **31**, **38**–**40**, **42**, and **43** (see Scheme II) were isolated from these aldol reactions.

Scheme II



In an effort to enhance the stability of the metal chelates **9** we examined other common metal cations with a small ionic radius similar to lithium (0.78 Å)[11] but with a greater positive charge. The most attractive candidates appeared to be Mg^{2+} (0.78 Å),[11] Zn^{2+} (0.69 Å),[11] and Al^{3+} (0.45 Å).[11] In each case, *anhydrous* salts ($MgBr_2$, $ZnCl_2$, $AlCl_3$) of these metals were readily available, and their effect as additives in the reaction of lithium enolates with aldehydes could be examined. In practice (see Table I and Experimental Section, Tables II and III) the addition of anhydrous $AlCl_3$ offered marginal benefit but the addition of either anhydrous $MgBr_2$ (formed as an etherate) or anhydrous $ZnCl_2$ resulted in the formation of aldol products in high yield at reaction temperatures (0–25°) convenient for preparative work. In general, yields were best when the solvent was Et_2O (or PhH if the metal enolate was soluble in this solvent) rather than THF or DME, presumably because of the diminished tendency for Et_2O to compete with the β-keto alkoxide **4** for coordination sites on the metal cation. The

(11) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 3rd ed, Interscience, New York, N. Y., 1972, p 52.

condensations were remarkably rapid; at 0°, all of the reactions examined were complete in less than 30 sec, and the use of prolonged reaction times served only to degrade the initially formed aldol products to form enones or other by-products. The choice between the anhydrous salts $MgBr_2$ and $ZnCl_2$ was made on the basis of experimental convenience. We found the quality of $MgBr_2$ best when it was prepared from magnesium metal (see Experimental Section) as needed; the solubility of this salt in the common ethereal solvents was relatively low. Commercial "anhydrous" $ZnCl_2$ was readily dehydrated by fusion under reduced pressure, and this anhydrous (freshly fused) salt was easily soluble in Et_2O (0.69 *M* at 23°) although less soluble in THF (0.35 *M* at 23°) or DME (0.05 *M* at 23°). Consequently, in all subsequent work we employed stock solutions of anhydrous $ZnCl_2$ (0.69 *M*) in Et_2O since these solutions were easily stored under anhydrous conditions and aliquots for addition to reaction mixtures were easily measured and transferred. The optimum quantity of $ZnCl_2$ proved to be (see Experimental Section Tables I and II) that amount needed to convert all of the alkoxide bases (RO^-) present to their zinc derivatives [$Zn(OR)_2$]. Thus, 1.0 mol of $ZnCl_2$ was added per mole of lithium enolate (and accompanying lithium *tert*-butoxide) formed from an enol acetate. When the lithium enolate was formed from the ketone and $(i\text{-Pr})_2NLi$ or from the trimethylsilyl enol ether and MeLi, then the optimum quantity was 0.5 mol of $ZnCl_2$/mol of enolate.

In summary, we conclude that the following reaction conditions should be employed to obtain optimum yield of aldol products from preformed lithium enolates.

(1) Higher yields of aldol products are normally obtained when the lithium enolate is generated in either Et_2O or DME from either an enol acetate and MeLi or the ketone and $(i\text{-Pr})_2NLi$. The relatively slow formation[9,12] of lithium enolates from the trimethylsilyl enol ethers and MeLi in nonpolar solvents complicates the use of this method.

(2) The aldol condensation should be effected in the relatively nonpolar solvent, Et_2O, or in Et_2O–DME mixtures whenever practical. Among the more polar solvents DME gave better results than THF.

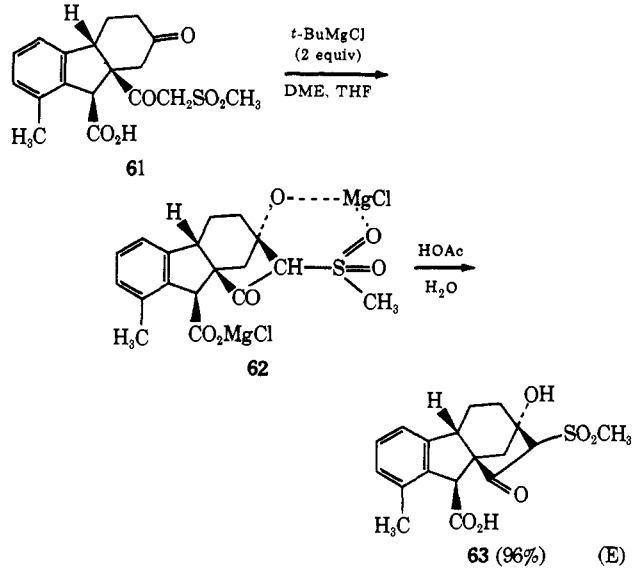
(3) Successful condensations with lithium enolates in the absence of added $ZnCl_2$ (or $MgBr_2$) can sometimes be achieved if the reactions are performed in Et_2O solution at low temperatures (−20 to −50°). If the more polar solvent DME (or THF) is used, then the addition of $ZnCl_2$ is almost always desirable.

(4) For reactions to be run at temperatures above −20°, it is most satisfactory to add freshly fused $ZnCl_2$ as a saturated solution in Et_2O (*ca.* 0.69 *M* at 23°) to a cold (−10 to 0°) solution of the lithium enolate. The optimum quantity of $ZnCl_2$ is that amount required to form $Zn(OR)_2$ salts of all strong bases (RO^-) in the reaction mixture. At relatively high concentrations, some LiCl may separate from the solution during this addition.

(5) The resulting cold (0°) solution (or suspension) should be treated with the second carbonyl component and then stirred at 0–10° for a *maximum reaction time* of 5 min.

(6) The aldol products are efficiently isolated by *adding the reaction solution* containing the metal chelates **9** (M = $\frac{1}{2}$ Zn^{2+}) *to* aqueous NH_4Cl followed by either crystallization of the crude product or chromatography on acid-washed silicic acid.[13] It should be emphasized that many of these aldol products are very labile to epimerization, reversal of the aldol condensation, or dehydration if they are allowed to stand in the presence of weak acids or bases.

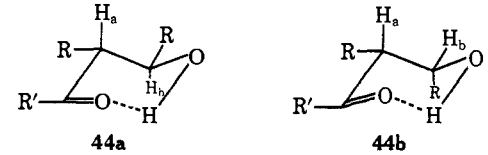
The application of this procedure to a variety of lithium enolates to form β-ketols is summarized in Table I. In other work,[7e] we have applied this same principle to an intramolecular aldol condensation (eq E). In this case, formation of the intermediate metal



61 → **62** → **63** (96%) (E)

chelate **62** was essential since treatment of the aldol product **63** with mild aqueous bases resulted in the quantitative conversion of **63** to the starting diketone **61**.

Stereochemistry of Aldol Products. The aldol condensations with ketones **33**, **46**, **53**, and **57** introduced the problem of forming varying amounts of two diastereoisomers (*e.g.*, stereoisomers **37a** and **37b** from ketone **33**). The problem of assigning stereochemistry to diastereoisomeric aldol products has been examined by several research groups,[2,5,7a–d,8,14] and the following conclusions may be drawn for the diastereoisomers in nonpolar aprotic solvents: (1) the two diastereoisomers exist as intramolecularly hydrogen bonded structures **44** with the six-membered ring containing the hydrogen bond in a chair conformation and with the maximum number of substituents R equatorial; (2) the threo isomer **44a** with fewer nonbonding steric



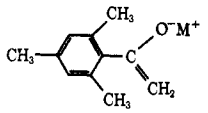
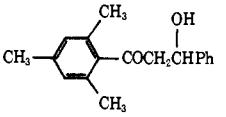
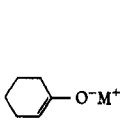
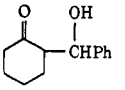
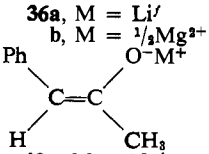
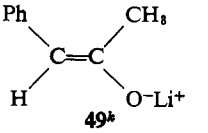
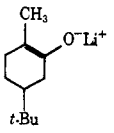
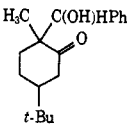
44a (threo isomer) **44b** (erythro isomer)

(12) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, 90, 4462, 4464 (1968).

(13) H. Brockmann and H. Muxfeldt, *Chem. Ber.*, 89, 1379 (1956).

(14) (a) M. Stiles, R. R. Winkler, Y. Chang, and L. Traynor, *J. Amer. Chem. Soc.*, 86, 3337 (1964); (b) J. E. Dubois and M. Dobois, *Bull. Soc. Chim. Fr.*, 3126 (1969); (c) J. J. Basselier, G. Gueremy, and S. Julia, *ibid.*, 2988 (1965); (d) E. Kiehlmann and P. W. Loo, *Can. J. Chem.*, 47, 2029 (1969).

Table I. Synthesis of β-Ketols from Metal Enolates

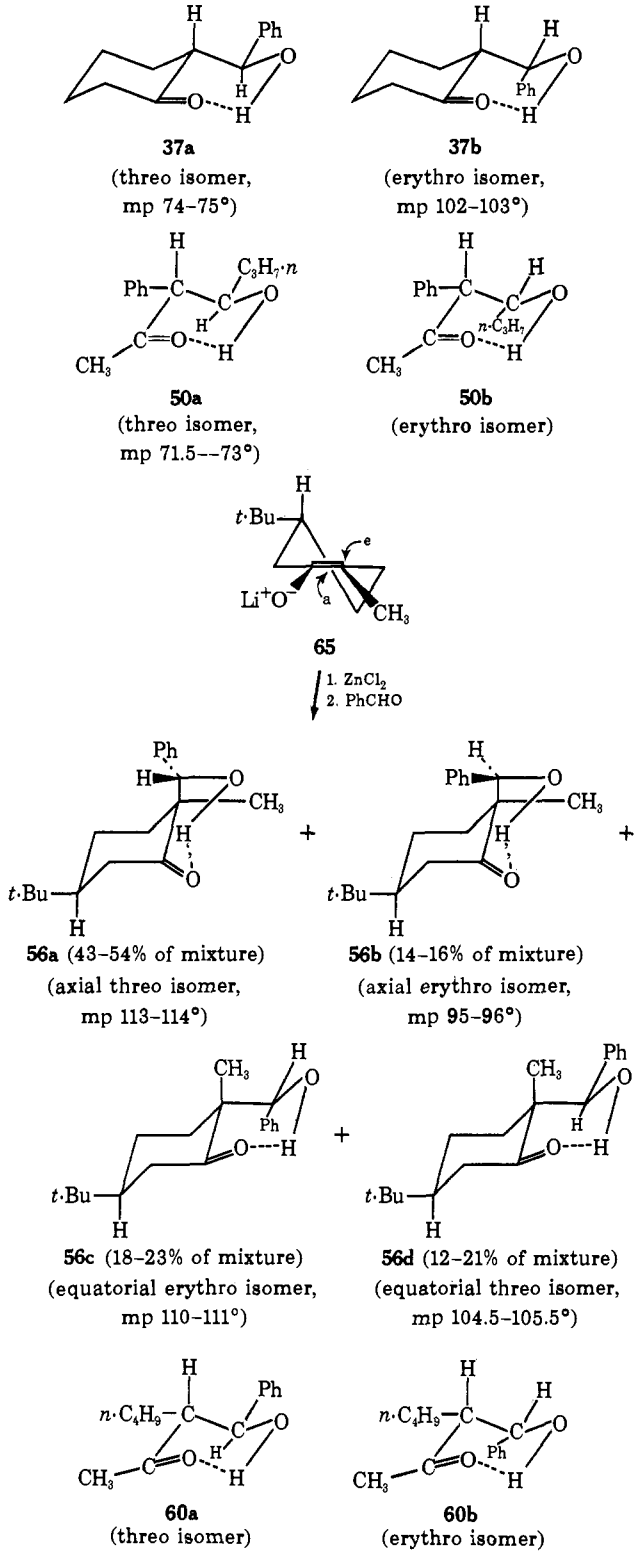
Metal enolate	Aldehyde	Reaction conditions	Additive (mol/mol of enolate)	Aldol product	Isolated yield, %
 **14a**, M = Li[a]	PhCHO	THF, −5°, 5 min		 **15**	16[b]
		THF, −5°, 5 min	$MgBr_2$ (1.0)	**15**	93
14b, M = MgBr[c]		PhH, 25°, 5 min		**15**	90
		Et_2O, 0–25°, 0.8–9 hr		**15**	20–34[d]
$PhC(O^-Li^+)=CH_2$ **19**[e]	PhCHO	THF, −35°, 10 min	$MgBr_2$ (1.01)	$PhCOCH_2C(OH)HPh$ **20**	81
t-$BuC(O^-Li^+)=CH_2$ **25**[f]	PhCHO	Et_2O, −50°, 5 min		t-$BuCOCH_2C(OH)HPh$ **26**	80
25[g]	t-BuCHO	Et_2O, −50°, 5 min		t-$BuCOCH_2C(OH)H$-t-Bu **27**	82
	t-BuCHO	Et_2O, 0°, 5 min	$ZnCl_2$ (1.0)	**27**	82
		DME, −3°, 5 min	$ZnCl_2$ (1.0)	**27**	78
 **36a**, M = Li[f] b, M = $^1/_2Mg^{2+}$	PhCHO	DME–Et_2O (1:2) 10°, 6 min	ZnCl (1.0)	 **37**	76[h]
 **48a**, M = Na[i] b, M = Li[g]	n-C_3H_7CHO	DME–Et_2O (1:2) 10°, 5 min	$ZnCl_2$ (1.0)	$PhCHCHC_3H_7$-n (COCH₃, OH) **50**	60[i]
		DME–Et_2O (1:2) 10°, 5 min	$ZnCl_2$ (1.0)	**50**	81
 **49**[k]	n-C_3H_7CHO	DME–Et_2O (1:2) 7°, 5 min	$ZnCl_2$ (0.5)	**50**	42[l]
 **54**[g]	PhCHO	DME–Et_2O (2:1) 1°, 5 min	$ZnCl_2$ (1.0)	 **56**	84
n-$BuCH=C(O^-Li^+)CH_3$ **59**[g]	PhCHO	DME–Et_2O (2:1) 15°, 2 min	$ZnCl_2$ (1.0)	n-$BuC(COCH_3)HC(OH)HPh$ **60**	80

[a] Obtained by reaction of the ketone with MeLi. [b] The major product was the enone **16**. [c] Obtained by reaction of the ketone with MeMgBr. [d] In one of these experiments, 6% of the diketone **17** was also isolated. [e] Obtained by reaction of the trimethylsilyl enol ether with MeLi. [f] Obtained by reaction of the ketone with $LiN(Pr\text{-}i)_2$. [g] Obtained by reaction of the enol acetate with MeLi. [h] The dialdol product **39** was also isolated in 10% yield. [i] Obtained by reaction of the ketone with NaH. [j] The enone **51** was also isolated in 20% yield. [k] The metal enolate used contained 60% of the cis isomer **49** and 40% of the trans isomer **48b**. [l] In this experiment, 25% of the dialdol product **52** and 5% of the enone **51** were also isolated.

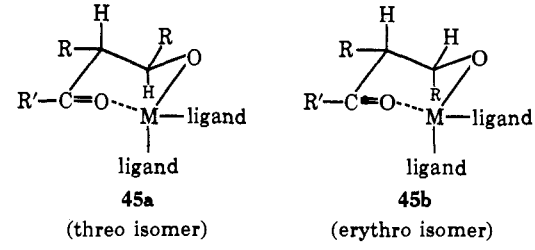
interactions, forms a stronger hydrogen bond with the result that the ir frequency difference, $\bar{\nu}_{free\,OH} - \bar{\nu}_{assoc\text{-}OH}$ is larger for **44a** than for **44b**; and (3) the nmr coupling constant, J_{ab}, is larger (typically 6–9 Hz) for the threo isomer **44a** (with trans diaxial protons H_a and H_b) than for the erythro isomer **44b** (typically 2–4 Hz). This coupling constant difference is diminished when the hydrogen bond is disrupted by acetylating the hydroxyl group or measuring the nmr spectrum in a protic solvent. Application of these criteria (see Experimental Section) to the diastereoisomers **37**, **50**, and **60** led us to the stereochemical assignments indicated in Scheme III. The erythro configuration **37b** is in agreement with the stereochemistry previously assigned[14c] to the diasteroisomer, mp 102–103°.

The stereochemical compositions of the aldol product **37** formed under various conditions are summarized in Table III (Experimental Section). Under equilibrating conditions (NaOH + H_2O) the two aldol stereoisomers were formed in comparable amounts (**37a**/**37b** = 1). As the reaction conditions were varied to favor the formation of stable metal chelates **45** in the condensation reaction, the proportion of the threo aldol **37a** (from chelate **45a**) increased to **37a**/**37b** ~ 4–5 when M = $^1/_2Zn^{2+}$ and the solvent was a DME–Et_2O mixture. In the condensation with phenylacetone (**46**, see Table I) in the presence of Zn^{2+} cation, we were able to compare the behavior of the trans sodium enolate **48a** (from **46** + NaH, **50a**/**50b** ~ 9) with the trans lithium enolate **48b** (from **47** + MeLi,

Scheme III



50a/50b ~ 9) and a mixture of lithium enolates containing about 60% cis enolate **49** and 40% trans enolate **48b** [from **46** + $(i\text{-Pr})_2$NLi, **50a/50b** ~ 6].[15a,b] The yield and stereospecificity of this reaction to form the threo aldol isomer **50a** were best when the trans lithium enolate **48b** (from the enol acetate **47**) was treated successively with ethereal $ZnCl_2$ and with butyraldehyde.



Samples of each of the four diastereoisomeric aldol products **56** from ketone **53** were isolated, and the stereochemical assignments indicated in Scheme III were made from a combination of physical and chemical properties described in the Experimental Section. The most compelling argument for assigning the axial configuration to aldol isomers **56a** and **56b** was provided by the fact that these two isomers underwent rapid retrograde aldol condensation on treatment with base under conditions where the two equatorial isomers **56c** and **56d** (and also the predominantly equatorial isomers **37a** and **37b**) were relatively stable. Since the structures of these isomers **56** precluded the use of the previously mentioned nmr coupling constant correlation, our assignments of erythro and threo configurations to the pair of axial isomers **56a** and **56b** and to the pair of equatorial isomers **56c** and **56d** must be regarded as tentative. However, we can conclude that reaction of the enolate **54** (or **65**) with benzaldehyde results in about 60–70% attack from the direction (labeled a in structure **65**) that introduces a new axial substituent. For comparison, in other studies[15c] both methylation of the enolate **54** (or **65**) with MeI and Michael addition to methyl acrylate under kinetically controlled conditions have been found to occur predominately (80–86%) from the direction labeled a (structure **65**) to form products with the new substituent in the axial position.

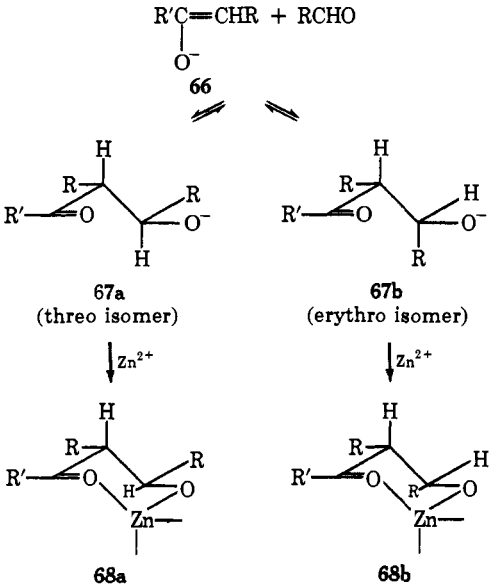
An analogous reaction procedure applied to the lithium enolate **59** produced the expected a mixture of diastereoisomeric aldol products **60** containing 45–52% of the threo isomer **60a** and 48–55% of the erythro isomer **60b**.

In each of the four cases (Table I and Scheme III) where mixtures of stereoisomeric aldol products resulted, we examined the composition of these mixtures after both relatively short (10–20 sec) reaction times and after reaction times of approximately 5 min. It was not practical to follow these reactions for relatively long periods of time because of the previously noted degradation of the initially formed aldol products which led to a variety of by-products. Within the time scale we could examine meaningfully, we observed little change in the stereoisomeric composition of the aldol products for any of the cases studied. These results are in contrast to the results of Dubois and coworkers[7d,8e–g] and of Hauser and coworkers[8d] who noted that the stereoisomeric mixture of aldol products obtained under conditions of kinetic control often changed with time. In general, the earlier results suggest that for *covalent metal enolates* the kinetically controlled product mixtures from cyclic enolates (or acyclic cis enolates) should favor the threo isomer, whereas the erythro isomer should be favored

(15) (a) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969); (b) H. O. House, R. A. Auerbach, M. Gall, and N. P. Peet, *ibid.*, **38**, 514 (1973); (c) H. O. House and M. J. Umen, *ibid.*, **38**, 2841 (1973).

in kinetically controlled condensation with acyclic trans enolates.[8d-g] In all of these cases, if equilibrium is achieved between *erythro*-**45b** and *threo*-**45a** metal chelates in an aprotic reaction medium, the more stable threo isomer **45a** with two equatorial substituents in the metal chelate ring[16] is expected (and found[8d,g]) to be favored.

We believe that the stereochemical results obtained in our reactions in the presence of Zn^{2+} reflect predominant equilibrium control as a result of rapid equilibration among the starting enolate **66** and the initially formed β-keto alkoxide anions **67**. The alkoxides **67** are removed from this equilibrating



mixture to form the zinc chelates **68** with a normal preference for the formation of the threo zinc chelate **68a** in which the substituents R are both equatorial. This point of view accommodates our observed lack of time dependence for the stereochemical composition, the formation of the same major stereoisomer **50a** from both cis and trans enolates **48b** and **49**, the substantially diminished percentage of "axial attack" in aldol condensation with the enolate **65** when compared with kinetically controlled alkylation, and our data presented elsewhere[15b] suggesting that zinc enolates of simple ketones are no more covalent than the corresponding sodium or lithium enolates in ethereal solvents.

Experimental Section[17]

Preparation of Enol Acetates and Trimethylsilyl Enol Ethers. A mixture of 30 g (0.25 mol) of acetomesitylene (**10**) [ir (CCl_4) 1700 cm^{-1} (C=O); nmr (CCl_4) δ 6.73 (2 H, s, aryl CH), 2.33 (6 H, s, two CH_3 groups), 2.23 (3 H, s, CH_3), and 2.16 (3 H, s, CH_3)], 1.5 g (8 mmol) of *p*-TsOH, and 52 g (0.52 mol) of isopropenyl acetate was heated under partial reflux for 24 hr with continuous distillation of materials boiling below 90°. The resulting mixture was diluted with 200 ml of pentane and poured into cold (0°) saturated aqueous $NaHCO_3$. Solid $NaHCO_3$ was added until neutralization of the HOAc was complete, and then the pentane solution and pentane extract of the aqueous phase were combined, dried, concentrated, and distilled. The crude distillate [33.5 g, bp 118–125° (10 mm), $n^{25}D$ 1.5142] was fractionally distilled through a 60-cm spinning band column to separate 12.2 g (30%) of the pure (glpc) enol acetate **13**, bp 122–123° (10 mm), $n^{25}D$ 1.5162, and 12.8 g of lower boiling fractions, bp 107–122° (10 mm), $n^{25}D$ 1.5073–1.5160, which contained (glpc, silicone fluid, No. 710, on Chromosorb P) mixtures of the ketone **10** (ret time 1.9 min) and the enol acetate **13** (12.9 min). The enol acetate **13** crystallized on standing and was recrystallized from pentane to separate the enol acetate **13** as white prisms: mp 35–36°;[17b] ir (CCl_4) 1755 (enol ester C=O) and 1655 cm^{-1} (enol C=C); uv maximum (isooctane) 235 mμ (shoulder, ε 7560) with intense end absorption (ε 33,700 at 203 mμ); nmr (CCl_4) δ 6.70 (2 H, s, aryl CH), 5.20 (1 H, d, J = 1.0 Hz, vinyl CH), 4.70 (1 H, d, J = 1.0 Hz, vinyl CH), 2.28 (6 H, s, two CH_3 groups), 2.20 (3 H, s, CH_3), and 2.00 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 204 (10, M^+), 147 (100), 144 (19), 119 (17), 45 (25), and 43 (84).

The same procedure was used with 75 g (0.75 mol) of pinacolone (**12**), 4.5 g (24 mmol) of *p*-TsOH, and 155 g (1.55 mol) of isopropenyl acetate to yield 30.1 g (28%) of the enol acetate **24**: bp 140–141°, $n^{25}D$ 1.4156 (lit.[18a] bp 136–137°, $n^{25}D$ 1.4144); ir (CCl_4) 1765 (enol ester C=O) and 1655 cm^{-1} (C=C); uv (95% EtOH) end absorption (ε 850 at 210 mμ); nmr (CCl_4) δ 4.80 (1 H, d, J = 1.5 Hz, vinyl CH), 4.60 (1 H, d, J = 1.5 Hz, vinyl CH), 2.10 (3 H, s, $COCH_3$), and 1.10 (9 H, s, $(CH_3)_3C$).

The same procedure with 120 g (1.00 mol) of acetophenone (**11**), 6.0 g (32 mmol) of *p*-TsOH, and 209 g (2.07 mol) of isopropenyl acetate yielded 52.7 g (33%) of α-acetoxystyrene (**18b**) as a colorless liquid: bp 120–122° (20 mm); $n^{25}D$ 1.5327 [lit.[16b] bp 89.5–90° (3 mm), $n^{25}D$ 1.5329]; ir (CCl_4) 1765 (enol ester C=O) and 1640 cm^{-1} (C=C); uv maximum (isooctane) 243 mμ (ε 12,200); nmr (CCl_4) δ 7.1–7.6 (5 H, m, aryl CH), 5.29 (1 H, d, J = 1.5 Hz, vinyl CH), 4.89 (1 H, d, J = 1.5 Hz, vinyl CH), and 2.05 (3 H, s, $COCH_3$).

A previously described procedure[9] was used with 49.0 g (0.50 mol) of cyclohexanone (**33**), 1.0 ml of aqueous 70% $HClO_4$, 153 g (1.5 mol) of Ac_2O, and 400 ml of CCl_4 to form the enol acetate **34** in 50% yield: bp 96–100° (43 mm); $n^{26}D$ 1.4560–1.4581 [lit.[19] bp 98° (48 mm), $n^{30}D$ 1.4541]; ir (CCl_4) 1755 (enol ester C=O) and 1685 cm^{-1} (enol C=C); nmr (CCl_4) δ 5.10 (1 H, m, vinyl CH), and 1.4–2.3 (11 H, m, CH_3 and CH_2); mass spectrum *m/e* (rel intensity) 140 (M^+, 5), 98 (83), 97 (20), 70 (77), 43 (100), and 41 (24).

Preparations described elsewhere were followed to obtain the following enol acetates and trimethylsilyl enol ethers: **18a**,[15a] **23**,[15a] **35**,[15a] **47**,[15a] **55**,[15c] and **58**.[9]

Preparation or Purification of Solvents, Metal Salts, and Organometallic Reagents. Reaction of 9.6 g (0.40 g-atom) of triply sublimed Mg (Dow Chemical Co.) with 46.0 g (0.20 mol) of Me_2Hg in approximately 50 ml of Et_2O followed by dilution with Et_2O and decantation afforded a colorless ether solution which was 0.91 *M* in Me_2Mg (yield *ca.* 90%). The reagent solution was standardized as previously described[20] employing a glpc column (silicone fluid, No. 710, on Chromosorb P) to analyze the mixture of $PhSiMe_3$ (ret time 12.0 min) and internal standard (cumene, 9.6 min).

A mixture of 4.8 g (0.20 g-atom) of triply sublimed Mg and 36.0 g (0.10 mol) of $HgBr_2$ in 400 ml of THF was stirred in an ice bath until the vigorous reaction subsided[21] and then refluxed for 4 hr. The mixture was allowed to settle, and the colorless solution was decanted, concentrated under N_2, and cooled to separate 29.3

(16) For a discussion of the applicability of conformational principles to metal chelates, see R. D. Gillard and H. M. Irving, *Chem. Rev.*, **65**, 603 (1965).

(17) (a) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 mHz with a Varian, Model A-60 or Model T-60, nmr spectrometer. The chemical shift values are expressed in δ values (ppm) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a Hitachi (Perkin-Elmer) or a Varian, Model M-66, mass spectrometer. All reactions involving anhydrous metal salts, strong bases, or organometallic intermediates were performed under a nitrogen atmosphere. (b) All new compounds that were isolated in pure form were analyzed for carbon and hydrogen. The results of these analyses, which were made available with this manuscript, agreed with the calculated values to within ±0.37% or less.

(18) (a) F. Iimura, *Nippon Kagaku Zasshi*, 77, 1846 (1956); *Chem. Abstr.*, **53**, 2779 (1957); (b) A. I. Bol'shukhin and V. L. Zhitorchuk, *J. Gen. Chem. USSR*, **25**, 1403 (1955).

(19) F. G. Young, U. S. Patent 2,461,016 (1949); *Chem. Abstr.*, **43**, 3838 (1949).

(20) H. O. House and W. L. Respess, *J. Organometal. Chem.*, **4**, 95 (1965).

(21) E. C. Ashby and R. C. Arnott, *J. Organometal. Chem.*, **14**, 1 (1968).

g of solvated $MgBr_2$. The material was recrystallized from THF and then dried under reduced pressure to leave 19.8 g of salt with an average molecular weight (Volhard titration for bromide ion) of 358 corresponding to $MgBr_2 \cdot 2.4C_4H_8O$.

Commercial $ZnCl_2$ (Mallinckrodt) was successively fused (2 or 3 times) under reduced pressure (0.1 mm) and then cooled under N_2. The anhydrous salt was either transferred to a reaction vessel under a nitrogen atmosphere or, preferably, dissolved in an anhydrous solvent to form a saturated solution. The concentrations of these solutions were determined by quenching aliquots in dilute aqueous NH_3 followed by EDTA titrations for Zn^{2+} to an Erichrome Black T endpoint. The saturated solutions had the following concentrations: Et_2O, 0.69 *M* at 23° or 0.17 *M* at 2°; THF, 0.35 *M* at 23 or 2°; DME, 0.05 *M* at 23° or 0.03 *M* at 2°. Anhydrous $AlCl_3$ (Baker and Adamson reagent grade) was either used without purification or was freshly sublimed at atmospheric pressure. Each of the ethereal solvents, Et_2O, THF, and DME, was freshly distilled from $LiAlH_4$ immediately before use. An Et_2O solution of MeMgBr, prepared from MeBr and triply sublimed Mg, was standardized by titrating aliquots with 2-butanol in xylene with 2,2′-bipyridyl as an indicator.[22] The same standardization procedure was used for commercial Et_2O solutions of MeLi (halide free, Foote Mineral Co.). As noted subsequently, several attempts to use commercial Et_2O solutions of MeLi from Alfa Inorganics, Inc. (or Lithium Corporation of America) (analysis 0.67 *M*[22] in MeLi and 2.3 *M* in halide ion by Volhard titration) led to complications from side reactions with an apparent large excess of MeLi. We believe these difficulties arose because the titration procedure[22] gives low values for the MeLi concentration when a large excess of lithium halide is present in the Et_2O solution.

Pivaldehyde. The following procedure was a significant improvement over previously described methods. A pentane solution (640 ml) containing 1.00 mol of *t*-BuLi was added, dropwise and with stirring over 2 hr, to 155 ml (146 g, 2.00 mol) of cold (0°) $(CH_3)_2NCHO$. The resulting solution was stirred overnight while it was allowed to warm to room temperature and then the pentane was removed under reduced pressure. Water (500 ml) was added to the residual solid, and the resulting mixture was acidified with 200 ml (2.4 mol) of aqueous 12 *M* HCl. The resulting solution distilled, and the fractions (2 phases) collected below 100° were combined and saturated with solid $NaHCO_3$. The organic layer was separated, dried, and distilled to separate 70 g (81%) of crude pivaldehyde, bp 65–80°. Redistillation through a 40-cm spinning band column afforded 59 g (69%) of pure pivaldehyde: bp 74–75°, $n^{25}D$ 1.3788 (lit.[23] bp 71–74°, $n^{20}D$ 1.3791); ir (CCl_4) 2710 (aldehyde CH), 1765 (weak), and 1725 cm^{-1} (C=O); nmr (CCl_4) δ 9.47 (1 H, s, CHO) and 1.05 (9 H, s, *t*-Bu).

Condensations with Acetomesitylene (10). Treatment of 2.00 ml of an Et_2O solution containing 3.8 mmol of MeLi with 620 mg (3.8 mmol) of the ketone **10** afforded the lithium enolate **14a** as a white precipitate that was insoluble in Et_2O and in PhH but was soluble in THF and in DME. When this mixture was quenched with H_2O and mixed with an internal standard (durene), analysis (glpc, silicone fluid, No. 710, on Chromosorb P) indicated the presence of the ketone **10** (ret time 21.6 min, recovery 82%) and durene (6.4 min). The addition of 600 mg (3.7 mmol) of the ketone **10** to 1.9 mmol of Me_2Mg in 2.0 ml of Et_2O initially formed a white precipitate which redissolved as all of the ketone was added to form a yellow solution. Removal of the ether under reduced pressure left the magnesium enolate (**14**, M = $\frac{1}{2}Mg^{2+}$) as a viscous yellow liquid which was soluble in PhH, Et_2O, THF, and DME. When an aliquot of the material was quenched with H_2O, analysis (glpc, with durene as an internal standard) indicated a 96% recovery of the ketone **10**. A PhH solution of the material exhibited nmr peaks at δ 4.92 (broad, vinyl CH), 4.0 (quartet, CH_2 of Et_2O), four singlets in the region 1.9–2.5, and 1.10 (triplet, CH_3 of Et_2O). The addition of 2.00 g (12.3 mmol) of the ketone **10** to 14.7 mmol of MeMgBr in 5.0 ml of Et_2O followed by removal of the Et_2O under reduced pressure left the bromomagnesium enolate **14b** as a white solid which was slightly soluble in PhH. When an aliquot of the PhH solution was quenched with H_2O and analyzed (glpc with durene as an internal standard), the concentration of enolate **14b** in PhH was found to be 0.174 *M*. As previously reported,[10] the nmr spectrum of this PhH solution had peaks at δ 4.50 (1 H, s, vinyl CH), 4.00 (1 H, s, vinyl CH), 2.50 (6 H, s, aryl CH_3), and 2.12 (3 H, s, aryl CH_3) as well as peaks at δ 3.50 (quartet, *J* = 7.0 Hz, CH_2 of Et_2O) and 1.05 (triplet, *J* = 7.0 Hz, CH_3 of Et_2O). When excess PhCHO was added to the solution and the nmr spectrum remeasured within 1–2 min, the above spectral peaks for enolate **14b** had disappeared and were replaced by a multiplet in the region of δ 1.50–2.30. The bromomagnesium enolate **14b**, from 0.81 g (5.0 mmol) of ketone **10** and 5.0 mmol of MeMgBr, in 1.7 ml of Et_2O was concentrated under reduced pressure and then dissolved in 30 ml of PhH. This solution was treated with 0.53 g (5.0 mmol) of PhCHO and then stirred for 5 min at 25° and partitioned between Et_2O and cold (0°), aqueous NH_3 and NH_4Cl (pH 8). The organic phase was washed with aqueous NaCl, dried, and concentrated. The residual yellow liquid (2.30 g) crystallized from hexane to separate 1.09 g (90%) of the ketol **15** as white needles: mp 76–77° (lit.[24] mp 77–77.5°);[17b] ir (CCl_4) 3500 (broad, assoc. OH) and 1695 cm^{-1} (C=O); uv maximum (95% EtOH) 252 mμ (ε 3560); nmr (CCl_4) δ 7.0–7.4 (5 H, m, aryl CH), 6.66 (2 H, s. aryl CH), 5.16 (1 H, t, *J* = 6 Hz, benzylic CHO), 3.45 (1 H, broad, OH, exchanged with D_2O), 2.6–3.0 (2 H, m, $COCH_2$), 2.20 (3 H, s, CH_3), and 2.10 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 268 (12, M^+), 250 (32), 162 (28), 159 (36), 148 (40), 147 (100), 146 (36), 120 (48), 119 (73), 106 (32), 105 (40), 91 (33), and 51 (22).

As summarized in Table I, a slurry of the bromomagnesium enolate **14b**, from 60 mmol of MeMgBr and 8.10 g (50 mmol) of ketone **10**, in 20 ml of cold (0°) Et_2O was treated with 5.30 g (50 mmol) of PhCHO and stirred for 45 min at 0° to yield 4.10 g (34%) of the ketol **15**, mp 75–76°. Repetition of this reaction with a reaction time of 9 hr at 25° afforded 3.60 g of a crude product which contained (tlc, silica gel with PhH–Et_2O eluent) the ketol **15** and the diketone **17**. A 1.0-g portion of this material was chromatographed on silica gel to separate 0.17 g (6%) of the diketone **17**, mp 130–132°, in fractions eluted with PhH and 0.74 g (20%) of the ketol **15**, mp 76–77°, in fractions eluted with PhH–Et_2O mixtures. The diketone was identified with the subsequently described authentic sample by comparison of nmr spectra.

To a cold (−10°) solution of the lithium enolate **14a**, from 0.54 g (3.3 mmol) of ketone **10** and 2.6 ml (5.0 mmol) of ethereal MeLi, in 5 ml of THF was added a solution of 5.2 mmol of $MgBr_2$ and 0.53 g (5.0 mmol) of PhCHO in 10 ml of THF. The resulting mixture was stirred at −5 to −10° for 5 min and then subjected to the usual isolation procedure to separate 0.74 g (93%) of the ketol **15**, mp 74–75°. When the reaction was repeated in the absence of $MgBr_2$, the yield of the ketol **15**, mp 75–76°, was 0.13 g (16%) and the ir spectrum of the mother liquors indicated the presence of substantial amounts of the unsaturated ketone **16**. Mesitylene was acylated ($AlCl_3$, CH_2Cl_2) with *trans*-cinnamoyl chloride to yield 82% of the crude unsaturated ketone **16**, bp 155–173° (0.55 mm) [lit.[25] bp 177–180° (2 mm)]. After recrystallization from hexane, 79% of the pure ketone **16** was obtained as yellow prisms: mp 58–59° (lit. mp 60–61°,[15a] 63°[26]); ir (CCl_4) 1650 (conj C=O) and 1625 cm^{-1} (conj C=C); uv maximum (95% EtOH) 295 mμ (ε 25,000); nmr (CCl_4) δ 7.1–7.6 (5 H, m, aryl CH), 6.5–7.1 (4 H, m, vinyl and aryl CH), 2.30 (3 H, s, CH_3), and 2.15 (6 H, s, two CH_3 groups).

A mixture of 3.0 g (12 mmol) of the unsaturated ketone **16** in 5 ml of Et_2O with the lithium enolate **14a**, from 2.0 g (12 mmol) of ketone **10** and 10 ml of an Et_2O solution containing 15 mmol of MeLi, was stirred at 25° for 3 hr and then poured into cold aqueous 1 *M* HCl. The solid that separated was collected, washed successively with aqueous $NaHCO_3$ and H_2O, and then recrystallized from EtOH to separate 1.8 g (37%) of the diketone **17** as white needles: mp 139–140° (lit.[27] mp 138–139°); ir ($CHCl_3$) 1700 cm^{-1} (C=O); uv maximum (95% EtOH) 250 mμ (ε 5900); nmr ($CDCl_3$) δ 7.1–7.4 (5 H, m, aryl CH), 6.77 (4 H, s, aryl CH), 3.9–4.2 (1 H, m, benzylic CH), 3.13 (4 H, d, *J* = 6.0 Hz, CH_2CO), 2.20 (6 H, s, CH_3), and 2.00 (12 H, s, CH_3); mass spectrum *m/e* (rel intensity) 412 (6, M^+), 251 (18), 146 (100), and 118 (27).

Condensation with Acetophenone (11). A cold (−40°) solution of the lithium enolate **19**, from 5.0 mmol of MeLi and 0.73 g (4.1 mmol) of the silyl enol ether **18**, in 10 ml of THF was treated with a solution of 5.0 mmol of $MgBr_2$ and 0.53 g (5.0 mmol) of PhCHO in 10 ml of THF. The resulting mixture was stirred at −35 to

(22) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

(23) K. N. Campbell, *J. Amer. Chem. Soc.*, **59**, 1980 (1937).

(24) R. C. Fuson, W. O. Fugate, and C. H. Fisher, *J. Amer. Chem. Soc.*, **61**, 2362 (1939).

(25) J. L. Guthrie and N. Rabjohn, *J. Org. Chem.*, **22**, 176 (1957).

(26) E. P. Kohler, *Amer. Chem. J.*, **38**, 553 (1907).

(27) R. C. Fuson and L. R. Melby, *J. Amer. Chem. Soc.*, **75**, 5402 (1953).

−50° for 10 min and then subjected to the usual isolation procedure. The residual liquid (0.94 g) crystallized from pentane to separate 0.77 g (81%) of the ketol **20**, mp 48–50°, identified with a subsequently described sample by comparison of nmr spectra.

To prepare an authentic sample of the ketol **20**,[28] a solution prepared by stirring 20.0 g (104 mmol) of $PhCOCH_2CO_2Et$ with 1.5 l. (150 mmol) of aqueous 0.1 *M* NaOH for 6 hr at 25° was freed from oxygen by passing N_2 through the solution for 30 min. Then the solution was neutralized (phenolphthalein end point) with aqueous 1.0 *M* HCl and treated with 100 ml of aqueous 0.1 *M* phosphate buffer (pH 7) and 3.0 g (29 mmol) of PhCHO. After the mixture had been stirred at 25° under an N_2 atmosphere for 20 days, it was extracted with Et_2O, and the ethereal extract was dried and concentrated. A 2.3-g portion of the crude product was chromatographed on silica gel to separate acetophenone in the early fractions (eluted with hexane–PhH and with PhH) and 1.15 g of the crude ketol **20** in later fractions (eluted with PhH–Et_2O). Recrystallization from pentane afforded 0.92 g of the ketol **20** as white prisms: mp 50–50.5° (lit.[28] mp 53–54°);[17b] ir (CCl_4) 3540 (assoc OH) and 1675 cm^{-1} (C=O); uv maximum (95% EtOH) 241 mμ (ε 13,200); nmr (CCl_4) δ 7.0–8.1 (10 H, m, aryl CH), 5.0–5.4 (1 H, t of d, *J* = 6.0 and 2.5 Hz, benzylic CHO), 3.43 (1 H, d, *J* = 2.5 Hz, OH, exchanged with D_2O), and 3.16 (2 H, d, *J* = 6.0 Hz, $COCH_2$); mass spectrum *m/e* (rel intensity) 120 (22), 106 (43), 105 (100), 77 (83), and 51 (31).

A solution of 10.0 g (48 mmol) of benzalacetophenone (**21**), 17 g (140 mmol) of acetophenone, and 20 ml (200 mmol) of aqueous 10 *M* NaOH in 100 ml of EtOH was refluxed for 15 min and then cooled and partitioned between H_2O and Et_2O. The residue from concentration of the organic phase crystallized from EtOH as 12.8 g of yellow solid which was recrystallized from an EtOH–HOAc mixture to separate 6.76 g (41%) of the diketone **22** as white needles: mp 83–84° (lit.[25,29] mp 85°); ir (CCl_4) 1687 cm^{-1} (C=O); uv maximum (95% EtOH) 241 mμ (ε 26,400); nmr (CCl_4) δ 7.0–8.1 (15 H, m, aryl CH), 3.7–4.1 (1 H, m, benzylic CH), and 3.0–3.5 (4 H, m, CH_2CO).

Condensation of Pinacolone (12). A. With Benzaldehyde. To a cold (−30°) solution of $(i\text{-Pr})_2NLi$ [from 25 mmol of MeLi and 25 mmol of $(i\text{-Pr})_2NH$] and a few milligrams of 2,2′-bipyridyl (an indicator) in 14.7 ml of Et_2O was added 2.5 g (25 mmol) of pinacolone (**12**). The resulting orange (excess R_2NLi) solution was cooled to −60° and 2.65 g (25 mmol) of PhCHO was added. The solution was stirred at −50 to −60° for 5 min and then partitioned between Et_2O and cold (0°), aqueous 1 *M* HCl. The organic layer was washed successively with aqueous $NaHCO_3$, with H_2O, and with aqueous NaCl and then dried and concentrated. Distillation of the residual liquid (5.67 g) in a short-path still separated 4.1 g (80%) of the ketol **26** as a colorless liquid, bp 86° (0.07 mm), $n^{25}D$ 1.5077. The ketol **26** crystallized from a hexane–pentane mixture as white prisms: mp 22–23°;[17b] ir (CCl_4) 3530 (assoc OH) and 1695 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ε 46–120) in the region 240–270 mμ with a maximum at 291 mμ (ε 85); nmr (CCl_4) δ 7.0–7.4 (5 H, m, aryl CH), 4.9–5.2 (1 H, m, benzylic CHO), 3.70 (1 H, d, *J* = 3.0 Hz, OH, exchanged with D_2O), 2.5–2.9 (2 H, m, CH_2CO), and 1.03 [9 H, s, $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 131 (100), 106 (28), 105 (28), 103 (25), 77 (41), 57 (53), 51 (20), and 43 (18).

B. With Pivaldehyde. A cold (−40°) solution of $(i\text{-Pr})_2NLi$, prepared at −10 to −30° from 5.0 mmol of MeLi and 0.55 g (5.5 mmol) of $(i\text{-Pr})_2NH$ in 3.0 ml of Et_2O containing 2,2′-bipyridyl (an indicator), was treated with 0.52 g (5.2 mmol) of pinacolone (**12**). The resulting pale orange solution was stirred at −60° for 15 min and then treated with 0.58 g (6.7 mmol) of pivaldehyde. The resulting light yellow solution was stirred at −50 to −60° for 5 min and then partitioned between ether and cold (0°) aqueous HCl and worked up in the usual way. The residual solid (1.03 g) was recrystallized from hexane to separate 0.76 g (82%) of the ketol **27** as white needles: mp 50–51°;[17b] ir (CCl_4) 3540 (broad, assoc OH) and 1695 cm^{-1} (C=O); uv maximum (95% EtOH) 287 mμ (ε 36); nmr ($CDCl_3$) δ 3.55 [1 H, d (*J* = 9.5 Hz) of t (*J* = 3 Hz), CHO], 3.08 (1 H, d, *J* = 3 Hz, OH, exchanged with D_2O), 2.2–2.8 (2 H, m, CH_2CO), 1.12 [9 H, s, $(CH_3)_3C$], and 0.88 [9 H, s, $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 111 (49), 57 (100), 55 (16), 43 (27), 41 (78), and 39 (22).

In a comparable reaction involving 27 mmol of $(i\text{-Pr})_2NLi$, 2.23 g (22.5 mmol) of pinacolone, and 1.95 g (22.5 mmol) of pivaldehyde in 17 ml of Et_2O, the reaction solution was added to a freshly filtered (to remove Et_3NH^+ Cl^-) solution of 8 ml (*ca.* 50 mmol) of Me_3SiCl and 6 ml of Et_3N in 20 ml of DME. The resulting reaction mixture was partitioned between pentane and aqueous $NaHCO_3$, and the pentane extract was washed successively with aqueous 1 *M* HCl, with aqueous $NaHCO_3$, and with aqueous NaCl and then dried and concentrated. The residual liquid (5.9 g), which contained (glpc, silicone gum, XE-60, on Chromosorb P) pivaldehyde (1.9 min), pinacolone (**12**, 7.0 min), the unsaturated ketone **28** (8.8 min), the hydroxy ketone **27** (17.2 min), and the silyl ether **29** (27.0 min), was fractionally distilled to separate 1.13 g of a fraction, bp 47–49° (7 mm), $n^{25}D$ 1.4323, which contained (glpc) primarily the silyl ether **29**. A collected (glpc) sample of **29**, a colorless liquid, was used for characterization:[17b] ir (CCl_4) 1710 cm^{-1} (C=O); uv maximum (95% EtOH) 285 mμ (ε 32); nmr (CCl_4) δ 3.92 (1 H, d of d, *J* = 8 and 3 Hz, CHO), 2.0–2.8 (2 H, m, CH_2CO), 1.08 [9 H, s, $(CH_3)_3C$], 0.83 [9 H, s, $(CH_3)_3C$], and 0.03 [9 H, s, $(CH_3)_3Si$]; mass spectrum *m/e* (rel intensity) 201 (11), 85 (32), 75 (26), 73 (21), 58 (100), and 41 (14).

To a cold (−60°) solution of 53 mmol of MeLi in 60 ml of Et_2O containing several milligrams of 2,2′-bipyridyl was added, dropwise and with stirring during 4 min, 3.567 g (25.1 mmol) of the enol acetate **24**. The resulting purple solution of lithium enolate **25** was stirred at −40° for 15 min and warmed to −6°, treated with 3.4 g (25 mmol) of freshly fused $ZnCl_2$, and stirred for 10 min. To the resulting light purple, heterogeneous mixture was added, dropwise and with stirring during 1 min, 2.687 g (31.3 mmol) of pivaldehyde. The resulting cold (0°) mixture was stirred for an additional 4 min and then worked up in the usual way. After an aliquot of the Et_2O solution had been mixed with a known weight of internal standard (durene), analysis (glpc) indicated the yield of aldol product **27** to be 88%. The remaining Et_2O solution was concentrated, and the residual oil (4.61 g) was crystallized from pentane at Dry Ice temperatures to separate 3.800 g (82%) of the hydroxy ketone **27**, mp 49–50°.

A cold (−40°), red solution of the enolate **25** was prepared in a similar manner from 52 mmol of MeLi and 3.494 g (24.1 mmol) of the enol acetate **24** in 60 ml of DME containing several milligrams of 2,2′-bipyridyl. The solution was warmed to −10° and treated with 3.4 g (25 mmol) of anhydrous $ZnCl_2$, and the resulting heterogeneous mixture was stirred at −10 to −3° for 10 min. Then 3.016 g (35 mmol) of pivaldehyde was added, dropwise and with stirring during 2 min, and the resulting solution was stirred for an additional 4 min at −10 to −3°. The previously described isolation procedure was followed; glpc analysis of the crude reaction product indicated an 86% yield of the hydroxy ketone. Crystallization of the crude product from cold pentane separated 3.466 g (78%) of the hydroxy ketone **27**, mp 49–50°.

Attempts to form the aldol product **27** (or **28**) by reaction of a refluxing solution of pinacolone (**12**) and pivaldehyde in THF with NaH led to various side reactions. In one case the high-boiling by-products of this reaction were crystallized from hexane to separate the diketone **30** (33% yield) as white crystals: mp 52–54° (lit.[30] mp 53°); ir (CCl_4) 1705 cm^{-1}; nmr (CCl_4) δ 2.0–2.8 (3 H, m, aliphatic CH), 1.10 [18 H, s, $(CH_3)_3C$], and 0.88 [9 H, s, $(CH_3)_3C$]. When a refluxing solution of pinacolone was allowed to react with excess NaH for 40 hr and then subjected to the usual isolation procedure, the aldol product **31** was isolated in 74% yield as a colorless liquid, bp 202–205° (lit. bp 196–197°,[31a] 203–204°[31b]); ir (neat) 1685 (conj C=O) and 1610 cm^{-1} (conj C=C).

A solution of 950 mg (5.1 mmol) of the hydroxy ketone **27** and 50 mg of TsOH in 50 ml of PhH was refluxed for 5 min and then cooled, filtered, and concentrated. The residue was sublimed (45° and 5 mm) to separate 735 mg (87%) of the trans ketone **28** as white needles, mp 42–44° (lit.[32] mp 44–44.5°), which was identified with a previously described[32] sample by comparison of ir spectra and a mixture melting point determination.

Study of Various Reaction Conditions for the Aldol Condensation of Pinacolone (12) with Pivaldehyde. The subsequently described glpc (silicone fluid, No. 710, on Chromosorb W) analyses employed

(28) C. Schöpf and K. Thierfelder, *Justus Liebigs Ann. Chem.*, **518**, 127 (1935).

(29) St. von Kostanecki and G. Rossbach, *Ber.*, **29**, 1488 (1896).

(30) K. Dimroth and W. Mach, *Angew. Chem., Int. Ed. Engl.*, 7, 460 (1968).

(31) (a) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Amer. Chem. Soc.*, 76, 2349 (1954); (b) J. Colonge, *Bull. Soc. Chim. Fr.*, 57 (1935); A. Bienvenüe and J. E. Dubois, *ibid.*, 391 (1969).

(32) K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, and D. K. Roe, *J. Amer. Chem. Soc.*, **92**, 2783 (1970).

Table II. Reaction of the Lithium Enolate **25** of Pinacolone with Pivaldehyde

Solvent	Additive (mol/mol of enolate)	Reaction time, min	Reaction temp, °C	Product yields: Aldol **27**, %	Enone **28**, %	Pinacolone **12**, %	Other,[a] %
Et_2O		5	−50	81–89		11–19	
Et_2O		5	0	99	<1	1	
Et_2O		5	22	54	9	7	
Et_2O	$MgBr_2$ (0.55)	5	25	80	12	1	
Et_2O	$AlCl_3$ (0.72)	5	28	42	4	19	
Et_2O	$ZnCl_2$	5	25	85		9	
	(1.0)	5	−5 to 0	88		3	~3
Et_2O	$ZnCl_2$	2–15	0	68–78		3–8	~6–10
	(2.2)	2–15	20	47–50	1	7–19	~14–22
THF		5	−50	87		17	
THF		5	20	31–32	37–69	2–19	
THF	$MgBr_2$ (1.0)	5	25	38	18	12	
THF	$AlCl_3$ (0.98)	5	25	35	5	18	
THF	$ZnCl_2$	5	21–30	55–69	6–11	12–20	
	(1.1)	15	21–30	42	20	14	
THF	$ZnCl_2$	2–15	0	37–44	2–3	12–13	~10–11
	(2.2)	2–5	20	23–28	4–6	18	~13–15
		15	20	12	12	13	~18
DME		5	0–5	65	3	6	
DME		5	20–24	56	21	4	~9
DME	$MgBr_2$ (1.2)	5	22–24	23	4	27	~20
DME	$AlCl_3$ (0.93)	5	21–24	37	15	7	~10
DME	$ZnCl_2$ (2.2)	2–15	0	60–67	3	4–13	~4–6
DME	$ZnCl_2$	2–5	20	25–30	3–5	12–13	~14–15
	(2.2)	15	20	17	11	11	~18
DME	$ZnCl_2$ (1.3)	5	20–25	77	3	8	~4
DME	$ZnCl_2$ (1.1)	5	−10 to 0	86		6	

[a] Unidentified components eluted (glpc) more slowly than the aldol product **3**.

glpc equipment calibrated with known mixtures of pinacolone **12** (ret time 5.5 min), the trans enone **28** (32.3 min), durene (internal standard, 36.0 min), and the hydroxy ketone **27** (40.7 min). For all of the small-scale product studies (Table II), commercial Et_2O solutions of MeLi (halide free) were used. Cold (−20 to −40°) solutions containing 8.2–10.5 mmol of MeLi and several milligrams of 2,2′-bipyridyl (an indicator) in 10–12 ml of the specified solvent were treated with 543–656-mg (3.82–4.62-mmol) samples of the enol acetate **24**, and the resulting red (DME) to purple (Et_2O) solution of the lithium enolate **25** was treated with any specified additive, warmed to the specified reaction temperature, treated with 427–602 mg (5.00–7.00 mmol) of pivaldehyde, and then stirred for the specified reaction period. The mixture was partitioned between Et_2O and a cold (0°) aqueous solution [either 1 *M* HCl or a mixture (pH 8) of NH_4Cl and NH_3]. A known weight of internal standard (*ca.* 440–550 mg of durene) was added to the Et_2O solution, and it was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and analyzed by glpc. Several sets of comparison experiments demonstrated that in this case the product analysis was not influenced by the use of either aqueous 1 *M* HCl or a pH 8 aqueous buffer to quench the reaction mixture.

Several analogous reactions were performed in which Et_2O solutions of MeLi containing excess lithium halide (analysis 0.67 *M* in MeLi and 2.3 *M* in halide) were employed. In all of these cases the aldol products **27** and **28** were accompanied by substantial (*ca.* 44% of the total product mixture) amounts of the diol **32** (glpc retention time 55.0 min, durene ret time 38.0 min). We presume this difficulty arose because these reactions were performed in the presence of excess MeLi. A collected (glpc) sample of the diol **32** was obtained as a crystalline solid, mp 82–90° (lit. 84–86°,[33] 92–93°,[34] 90–91°[35]), that is evidently a mixture of diastereoisomers. This material was identified with a subsequently authentic sample of the diol **32** by comparison of ir, nmr, and mass spectra and glpc retention times.

Reaction of 501 mg (2.68 mmol) of the hydroxy ketone **27** with 5.40 mmol of MeLi in 10 ml of Et_2O at 4–9° for 1 hr followed by use of the previously described isolation procedure yielded 548 mg of crude diol **32**, mp 92–94°. Fractional crystallization of this mixture from Et_2O–pentane mixtures separated 234 mg of one stereoisomer of the diol **32** as white needles: mp 115–115.5°;[17b] ir (CCl_4) 3610 (OH) and 3500 cm^{-1} (broad, assoc OH); nmr ($CDCl_3$ + D_2O) δ 3.63 (1 H, d of d, J = 9.5 and 1.8 Hz, CHO), 1.97 (1 H, d of d, J = 15 and 1.8 Hz, part of CH_2), 1.30 (1 H, apparent d of d with J = 15 and 9.5 Hz, part of CH_2), 1.23 (3 H, s, CH_3), 0.95 (9 H, s, *t*-Bu), and 0.90 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 187 (2), 169 (9), 145 (12), 127 (100), 109 (56), 101 (80), 87 (56), 85 (41), 84 (40), 83 (60), 71 (40), 69 (44), 59 (43), 57 (71), 43 (59), and 41 (38).

The mother liquors from this fractional crystallization were crystallized from pentane to separate prisms, melting over the range 81–98°, with spectroscopic properties similar to those of the pure isomer described above.

Condensation with Cyclohexanone (33). To a cold (5°) solution of 51 mmol of MeLi and several milligrams of 2,2′-bipyridyl indicator in 20 ml of DME was added, dropwise and with stirring during 4 min, 3.790 g (25.0 mmol) of the enol acetate **34**. After this solution had been stirred for 5 min, 37.3 ml of an Et_2O solution containing 25 mmol of anhydrous $ZnCl_2$ was added, dropwise and with stirring during 1 min. The resulting heterogeneous mixture, from which a white granular solid slowly separated, was stirred for 8 min and cooled to 5°. Benzaldehyde (2.628 g or 24.8

(33) E. Yoshisato and S. Tsutsumi, *J. Amer. Chem. Soc.*, **90**, 4488 (1968).

(34) H. J. Shine and E. E. Turner, *J. Inst. Petrol., London*, **36**, 73 (1950).

(35) H. J. Backer and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **56**, 1069 (1937).

Table III. Aldol Condensation of Cyclohexanone (**33**) with Benzaldehyde

Source of enolate **36**	Solvent	Additive (mol/mol of enolate)	Reaction time	Reaction temp, °C	Product yield, %[a] Aldol **37**	Dialdol **39**	Aldol composition— Ratio[b] **37a/37b**	Isolated yields, %[c] **37a**	**37b**
33 + NaOH	H_2O		25 hr	25	62	2	1/1	7	18
34 + Me_2Mg	Et_2O		3 hr	25	23	*d*	*e*	8	15
34 + MeLi	DME		3 hr	25	20	*f*	*e*	3	17
33 + (*i*-Pr)$_2$NLi	DME		5 min	−20	67	5	1/1	23	27
33 + (*i*-Pr)$_2$NLi	DME	$ZnCl_2$ (1.0)	5 min	−5	60	7	3/1	31	8
33 + (*i*-Pr)$_2$NLi	DME-Et_2O (1:2)	$ZnCl_2$ (1.0)	5 min	8	46	7	4/1	20	5
33 + (*i*-Pr)$_2$NLi	DME-Et_2O (1:1)	$ZnCl_2$ (0.5)	5 min	12	57	9	4/1	35	8
34 + MeLi	DME	$ZnCl_2$ (1.0)	5 min	−2	65	8	2/1	26	24
34 + MeLi	DME-Et_2O (1:2)	$ZnCl_2$ (1.0)	6 min	10	76	10	4/1	36	11
35 + MeLi	DME		5 min	5	47[g]	14	2/1	22	12
35 + MeLi	DME-Et_2O (1:2)	$ZnCl_2$ (1.0)	5 min	7	53	1	4/1	25	7
35 + MeLi	DME-Et_2O (1:1)	$ZnCl_2$ (0.5)	5 min	14	59	16	5/1	43	8

[a] These yields were determined from the weights of chromatographic fractions. [b] These composition estimates were obtained from the nmr spectra of the crude products before chromatography. [c] The values are the yields of pure aldol stereoisomers **37a** and **37b** isolated by chromatography and fractional crystallization. [d] Other products isolated included 24% of the enone **38** and 35% of a mixture of components believed to be **42** and **43**. [e] Nmr analysis was not performed on this crude reaction mixture. [f] Other products isolated included 15% of the enone **38** and 62% of a mixture of **42** and **43**. [g] The enone **38** was isolated in 4% yield.

mmol) was added dropwise and with stirring during 1.5 min and the resulting solution (temperature 10°) was stirred for an additional 4.5 min and then subjected to the usual isolation procedure.

The nmr spectrum ($CDCl_3$) of the crude reaction product, 5.69 g of light yellow liquid, indicated the ratio threo isomer **37a**/erythro isomer **37b** to be 4:1; this analysis was based on the benzylic CH peak areas at δ 5.33 (from **37b**) and 4.80 (for **37a**). A solution of the crude product in Et_2O–hexane (1:4 v/v) deposited 384 mg (5%) of the crude dialdol product **39**, mp 150–155°. Chromatography of the remaining material on acid-washed silicic acid[13] with Et_2O–hexane (3:7 v/v) as an eluent separated 346 mg of early fractions containing (tlc, silica gel) the enone **38** and other components followed by 893 mg of the crude erythro isomer **37b**, mp 85–90°, 851 mg of a mixture (tlc) of aldols **37a** and **37b**, and 2.082 g of the crude threo isomer **37a**, mp 58–60°. Continued elution with a 1:1 (v/v) Et_2O–hexane mixture separated an additional 69 mg of threo isomer **37a** followed by 418 mg of the crude dialdol product **39**, mp 150–153°. Thus, the total yield of aldol products **37** was 3.895 g (76%) and the total yield of dialdol products **39** was 802 mg (10%). Recrystallization of appropriate chromatographic fractions from Et_2O–hexane mixtures separated 548 mg (11%) of **37b**, mp 100–102°, 1.811 g (36%) of **37a**, mp 71–74°, and 522 mg (7%) of fractions melting within the range 158–175° that contained varying amounts of the diastereoisomers of dialdol **39**.

Recrystallization from Et_2O–hexane separated the pure erythro aldol isomer **37b** as white needles: mp 102–103° (lit. mp 101–102°,[36a] 105.5–107°[36b]);[17b] ir (CCl_4) 3570 (assoc OH) and 1702 cm^{-1} (C=O). In dilute (0.005 *M*) CCl_4 solution, peaks attributable to free and intramolecularly associated OH stretching are located at 3616 and 3578 cm^{-1} (lit.[14c] 3615 and 3578 cm^{-1}), corresponding to $\Delta\bar{\nu}$ = 38 cm^{-1}; uv (95% EtOH) series of weak maxima (ϵ 115–237) in the region 240–270 mμ with a maximum at 290 mμ (ϵ 80); nmr (CCl_4) δ 7.0–7.5 (5 H, m, aryl CH), 5.30 (1 H. m, benzylic CH, collapsed to doublet, J = 2.4 Hz, when D_2O added), 2.82 (1 H, d, J = 3 Hz, OH, exchanged with D_2O), and 1.3–2.8 (9 H, m, aliphatic CH). In C_6D_6 solution the benzylic CH multiplet is located at δ 5.38; in CH_3OD solution the benzylic CH doublet is at δ 5.25 with J = 4.3 Hz and addition of D_2O increases the coupling constant to J = 5.0 Hz; mass spectrum *m/e* (rel intensity) 106 (100), 105 (96), 98 (41), 77 (92), 70 (22), 69 (29), 55 (79), 51 (38), 42 (51), 41 (25), and 39 (22).

Ketene was passed through a solution of 451 mg (2.21 mmol) of the erythro aldol **37b** and 1 drop of H_2SO_4 in 60 ml of $CHCl_3$ for 2 hr, and the resulting solution was washed successively with H_2O and with aqueous $NaHCO_3$ and then dried and concentrated. A solution of the crude residual liquid (786 mg) in Et_2O–hexane deposited 321 mg (59%) of the crude *O*-acetyl derivative, mp 65–67°. Recrystallization from Et_2O–hexane afforded 213 mg of the pure *erythro*-2-(α-acetoxybenzyl)cyclohexanone as white prisms; mp 68–69° (lit. mp 64–65°,[14c] 70.4–71°[37]); ir (CCl_4) 1754, 1743 (ester C=O), and 1716 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ϵ 58–208) in the region 240–270 mμ with a maximum at 286 mμ (ϵ 37); nmr (CCl_4) δ 7.1–7.4 (5 H, aryl CH), 6.13 (1 H, d, J = 5.4 Hz, benzylic CH), and 1.3–2.8 (12 H, m, aliphatic CH with CH_3CO singlet at δ 1.95); mass spectrum *m/e* (rel intensity) 246 (1, M^+), 204 (14), 203 (74), 187 (30), 186 (100), 185 (80), 107 (38), 105 (54), 98 (44), and 43 (22).

Recrystallization from Et_2O separated the pure threo aldol isomer **37a** as white needles: mp 74–75°;[17b] ir (CCl_4) 3545 (assoc OH) and 1700 cm^{-1} (C=O). In dilute (0.005 *M*) CCl_4 solution, peaks attributable to free and associated OH stretching are located at 3616 and 3548 cm^{-1} corresponding to $\Delta\bar{\nu}$ = 68 cm^{-1}; uv (95% EtOH) series of weak maxima (ϵ 102–227) in the region 240–270 mμ with a maximum at 288 mμ (ϵ 61); nmr (CCl_4) δ 7.1–7.4 (5 H, aryl CH), 4.68 (1 H, d of d, J = 3 and 8.4 Hz, benzylic CH, collapsed to doublet, J = 8.4 Hz, with added D_2O), 3.65 (1 H, d, J = 3 Hz, OH, exchanged with D_2O), and 1.2–2.8 (9 H, m, aliphatic CH). In C_6D_6 solution the benzylic CH signal is located at δ 4.80, J = 8.4 Hz; in CH_3OD solution this signal is at δ 4.95, J = 8.5 Hz, and addition of D_2O increases the coupling constant to J = 9.0 Hz; mass spectrum *m/e* (rel intensity) 106 (100), 105 (98), 98 (40), 77 (92), 70 (21), 69 (28), 55 (82), 51 (35), 42 (49), 41 (24), and 39 (20).

Reaction of 453 mg (2.22 mmol) of the threo aldol **37a** with ketene by the previously described procedure followed by crystallization of the crude product (618 mg) from Et_2O–hexane separated 342 mg (64%) of the crude *O*-acetyl derivative, mp 70–71°. Recrystallization (Et_2O–hexane) afforded the pure *threo*-2-(α-acetoxybenzyl)-cyclohexanone as white needles: mp 72–73°;[17b] ir (CCl_4) 1756 (sh), 1744 (ester C=O), and 1718 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ϵ 61–232) in the region 240–270 mμ with a maximum at 286 mμ (ϵ 43); nmr (CCl_4) δ 7.1–7.5 (5 H, m, aryl CH), 6.00 (1 H, d, J = 8.9 Hz, benzylic CH), and 1.2–3.0 (12 H, m, aliphatic CH with CH_3CO singlet at 1.91); mass spectrum *m/e* (rel intensity) 246 (1, M^+), 204 (13), 203 (84), 187 (39), 186 (100), 185 (81), 115 (51), 107 (83), 105 (62), 98 (83), 91 (50), and 43 (54).

Fractional crystallization of the mixture of diastereoisomeric dialdol products **39** from Et_2O–hexane separated one diastereoisomer of the dialdol **39** as white needles: mp 172–173° (lit.[37] mp 164–165°); ir (KBr pellet) 3500 (br, assoc OH) and 1690 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ϵ 240–406) in the region 240–270 mμ with a maximum at 291 mμ (ϵ 110); nmr ($CDCl_3$) δ 7.1–7.5 (10 H, m, aryl CH), 4.93 (2 H, m, benzylic CH), 3.5

(36) (a) G. Kresze and B. Gnauck, *Z. Electrochem.*, **60**, 174 (1956); (b) H. E. Zimmerman and J. English, Jr., *J. Amer. Chem. Soc.*, **76**, 2285 (1954).

(37) D. Vorlander and K. Kunze, *Ber.*, **59**, 2078, 2081 (1926).

(2 H, m, OH, exchanged with D_2O), and 1.1–3.1 (8 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 273 (1), 272 (1), 186 (16), 106 (100), 105 (81), 98 (50), 77 (73), and 51 (25).

As summarized in Table III, solutions of the lithium enolate **36a**, prepared in the usual way[9] from the enol acetate **34**, from the trimethylsilyl enol ether **35**, or from the ketone **33** and $(i\text{-Pr})_2NLi$, were allowed to react with PhCHO employing the same procedures for reaction, isolation, and analysis described above. In one run involving the lithium enolate **36a** obtained from the silyl ether **35**, aliquots removed after 20 sec and after 5 min contained (nmr analysis) 79 and 83%, respectively, of the threo isomer **37a** in the aldol product **37**. In reactions where Et_2O was not the cosolvent, solid anhydrous $ZnCl_2$ was added to the enolate solutions. The product yields from these reactions are tabulated in Table III. The early fractions from chromatography of these various reaction mixtures were combined and rechromatographed on acid-washed silicic acid with various hexane–PhH mixtures as the eluent. After elution of one or more unknown liquid components, the dibenzal ketone **40** was eluted with PhH. Recrystallization (Et_2O–hexane) of these fractions afforded the pure dienone **40**, mp 115–116° (lit.[37] mp 117–118.5), which was identified with an authentic sample by comparison of ir and nmr spectra. Subsequent chromatographic fractions contained the crude benzal ketone **38**, identified with an authentic sample by comparison of ir and nmr spectra.

A cold (0°) solution of the magnesium enolate **36b**, from 10 mmol of Me_2Mg and 1.398 g (10 mmol) of the enol acetate **34**, in 15.7 ml of Et_2O was treated with 1.186 g (11.1 mmol) of PhCHO, and the resulting mixture was stirred at 25° for 3 hr and then partitioned between pentane and dilute aqueous HCl. The crude organic product (1.94 g) was chromatographed on silica gel to separate, in order of elution with PhH–Et_2O, 550 mg (35%) of a mixture of subsequently described products **42** and **43**, 380 mg (24%) of the benzal derivative **38** (mp 54–56°), 230 mg (15%) of the aldol product **37b**, mp 101–103°, and 120 mg (8%) of the aldol product **37a**, mp 70–74°.

When this reaction procedure was repeated with a solution of the lithium enolate **36a**, from 21 mmol of MeLi and 1.294 g (9.3 mmol) of enol acetate **34**, in 15 ml of DME and 1.172 g (11 mmol) of PhCHO, chromatography separated 840 mg (62%) of a mixture of products **42** and **43**, 55 mg (15%) of the benzal ketone **38**, mp 54–56°, 225 mg (17%) of the aldol **37b**, mp 101–103°, and 40 mg (3%) of the aldol **37a**, mp 71–74°.

The chromatographic fractions containing (tlc, silica gel coating with a PhH eluent) at least three components believed to be isomers of **42** and **43** were combined and chromatographed on silica gel with PhH–hexane mixtures as eluents. A partially purified sample of the more rapidly eluted component, thought to be **42**, was recrystallized from EtOH to separate yellow needles, mp 83–85°, while the later fractions afforded a mixture containing (tlc) two materials, believed to be stereoisomers of structure **43**, which crystallized from EtOH as an orange solid, mp 60–75°. The crude product **42** (mp 83–85°) had the following properties: ir (CCl_4) 1645 (C=O) and 1610 cm^{-1} (C=C); uv maxima (95% EtOH) 238 mμ (ε 11,300) and 287 mμ (ε 1300); nmr ($CDCl_3$) δ 7.0–7.5 (multiplet, aryl CH) and 0.9–3.7 (multiplet, aliphatic CH); mass spectrum *m/e* (rel intensity) 277 (6), 274 (10), 273 (11), 266 (8, M^+ for **42**), 189 (24), 112 (24), 108 (92), 107 (77), 105 (25), 91 (38), 79 (100), 77 (66), 67 (20), 57 (44), 55 (24), 51 (32), 43 (46), and 41 (32).

The mixture of at least two components (tlc), which may be the stereoisomers of structure **43**[38] (mp 60–75°), has the following properties: ir (CCl_4) 3590, 3430 (broad) (unassoc and assoc OH), 1710 (w), 1685 (w), 1640 (C=O), and 1610 cm^{-1} (C=C); uv maximum (95% EtOH) 294 mμ (ε 10,200); nmr ($CDCl_3$) δ 7.0–7.5 (multiplet, aryl CH) and 0.8–3.3 (multiplet, aliphatic CH); mass spectrum *m/e* (rel intensity) 274 (7), 273 (8), 186 (56), 185 (63), 129 (28), 117 (28), 115 (37), 107 (31), 106 (32), 105 (65), 97 (29), 91 (36), 85 (36), 83 (30), 81 (27), 77 (53), 71 (59), 69 (39), 67 (41), 57 (100), 56 (33), 55 (56), 51 (27), 43 (84), and 41 (62).

In another reaction a solution of the lithium enolate **36a**, obtained from 25 mmol of MeLi and 3.778 g (19.9 mmol) of the silyl enol ether **35**, in 60 ml of DME was treated with excess (10.9 g, 103 mmol) PhCHO. The resulting mixture, from which a yellow precipitate separated, was stirred at 25° for 2 hr and then partitioned between aqueous HOAc and pentane. The Et_2O layer was washed with aqueous $NaHCO_3$, dried, and concentrated. The PhCHO [6.03 g, bp 72–75° (30 mm)] was distilled from the mixture to leave 5.10 g (94%) of crude dibenzal ketone **40**. This material was recrystallized from MeOH to separate 2.20 g (40%) of 2,6-dibenzalcyclohexanone (**40**) as yellow needles, mp 115–117.5° (lit.[37] mp 117–118.5°), identified with an authentic sample by comparison of ir spectra.

To a mixture of 20.0 g (0.20 mol) of cyclohexanone, 10.6 g (0.10 mol) of PhCHO, 14.0 g of $MgSO_4 \cdot 7H_2O$, and 1250 ml of H_2O was added a solution of 4.0 g (0.1 mol) of NaOH in 250 ml of H_2O. After the resulting mixture had been stirred for 20 hr and then allowed to stand for 36 hr, the resulting white precipitate was collected, dried, and continuously extracted with Et_2O. Concentration of this extract left 15.45 g of white solid that contained (nmr analyses) approximately equal amounts of the aldol isomers **37a** and **37b**. The previously described chromatographic and fractional crystallization procedures separated 3.594 g (18%) of the erythro aldol **37b**, mp 100–103°, 1.359 g (7%) of the threo aldol **37a**, mp 72–74°, and 251 mg (1%) of a mixture of diastereoisomers of the dialdol product **39**, mp 162–170°.

Condensation with Phenylacetone (46). After 35 g (*ca.* 0.8 mol) of NaH dispersion in mineral oil had been washed with pentane, 300 ml of DME was added and the suspension was cooled to 5°. Then 65.3 g (0.485 mol) of the ketone **46** was added dropwise and with stirring over 2 hr and the resulting mixture was allowed to stand 16 hr. The resulting supernatant solution contained (nmr analysis[15]) the sodium trans enolate **48a**; titration for total base indicated the solution to be 1.6 *M* in enolate.

To 18.8 ml of a DME solution containing 25.0 mmol of the sodium enolate **48a** was added 37.5 ml of an Et_2O solution containing 25.0 mmol of anhydrous $ZnCl_2$. The resulting mixture (two phases) was stirred for 15 min and cooled to 5° and then 1.82 g (25.0 mmol) of butyraldehyde was added dropwise and with stirring during 1 min. The resulting mixture was stirred at 5–10° for 4.5 min and then worked up in the usual way.

A solution of the residual liquid product (5.20 g) in pentane deposited 2.584 g of the crude threo aldol **50a**, mp 35–60°. Recrystallization from pentane afforded 2.205 g (43%) of the pure threo isomer **50a** as white needles: mp 71.5–73°;[17b] ir (CCl_4) 3540 (assoc OH) and 1705 cm^{-1} (C=O). Even in dilute (0.002–0.005 *M*) solution in CCl_4, only a broad peak at 3595 cm^{-1} attributable to an intramolecularly associated OH group was observed; uv (95% EtOH) series of weak (ε 300 or less) maxima in the region 240–270 mμ with a maximum at 286 mμ (ε 345); nmr (CCl_4) δ 7.1–7.5 (5 H, m, aryl CH), 4.0–4.4 (1 H, m, CHO), 3.65 (1 H, d, J = 9.5 Hz, benzylic CH), 3.35 (1 H, s, OH, exchanged with D_2O), 2.03 (3 H, s, CH_3CO), and 0.6–1.9 (7 H, m, aliphatic CH). In CH_3OD solution the benzylic CH doublet is located at δ 3.58 with J = 10.0 Hz and in C_6H_6 solution this doublet (J = 9.5 Hz) is at δ 3.57; mass spectrum *m/e* (rel intensity) 206 (0.1, M^+), 188 (8), 146 (20), 135 (26), 134 (100), 117 (52), 92 (48), 91 (76), 65 (31), 44 (36), and 43 (60).

The mother liquors were chromatographed on acid-washed silicic acid[13] with Et_2O–hexane mixtures as eluents to separate successively 919 mg (20%) of the crude liquid enone **51**, intermediate fractions containing (tlc) mixtures of the enone **51**, the ketone **46**, and the erythro aldol **50b**, 302 mg (6%) of the liquid erythro aldol **50b**, crystalline fractions containing (tlc) increasing amounts of the threo aldol **50a**, and 85 mg (1%) of a liquid containing (tlc) a mixture of diastereoisomeric dialdol products **52**. Recrystallization of appropriate fractions from pentane separated additional amounts of the threo aldol isomer **50a**, mp 71.5–73°, total yield 2.757 g (54%).

The fractions containing the liquid enone **51** exhibited a single glpc peak on three different columns and had spectroscopic properties indicating the presence of a single stereoisomer with the stereochemistry indicated in structure **51**. A collected (glpc, silicone fluid No. 710 on Chromosorb P) sample of the pure enone **51** was obtained as pale yellow liquid: $n^{25}D$ 1.5620;[17b] ir (CCl_4) 1694, 1676 (conj. C=O), and 1621 cm^{-1} (conj. C=C); uv (95% EtOH) broad maximum at 215 mμ (ε 13,000); mass spectrum *m/e* (rel intensity) 188 (18, M^+), 145 (11), 97 (30), 58 (68), 43 (100), and 40 (62); nmr (CCl_4) δ 6.9–7.5 (5 H, m, aryl CH), 6.76 (1 H, t, J = 7.2 Hz, vinyl CH), 0.7–2.5 (10 H, m, aliphatic CH with CH_3CO singlet at 2.10). The δ values were observed as increasing amounts of the lanthanide shift reagent, Eu (fod)$_3$, were added to 0.5 ml of the CCl_4 solution. After addition of 28 mg of Eu(fod)$_3$ the shifts observed were: 74 Hz for the CH_3CO singlet, 65 Hz for the vinyl CH triplet, 21 Hz for the allylic CH_2 multiplet, and 4 Hz for the CH_3 multiplet. Thus, we conclude that the coordinating group (CH_3CO)

(38) An authentic sample of one stereoisomer of structure **43** is reported to melt at 210°: S. Julia and D. Veresch, *Bull. Soc. Chim. Fr.*, 1127 (1959). This same material, mp 207–209°, has been studied subsequently: M. N. Tilichenko and V. G. Kharchenko, *Zh. Obshch. Khim.*, 29, 1909 (1959); *Chem. Abstr.*, 54, 9793 (1960); J. Pitha, M. N. Tilichenko, and V. G. Kharchenko, *ibid.*, 34, 1936 (1964); *Chem. Abstr.*, 61, 8163 (1964).

is closer in space to the vinyl CH than to the allylic CH_2 and assign the stereochemistry indicated in structure **51**.

The crude erythro aldol isomer **50b** was repeatedly precipitated from a pentane solution at −78° and the resulting liquid was distilled in a short-path still (0.1 mm and 120°) to separate the erythro aldol **50b** as a colorless liquid: $n^{25}D$ 1.5100;[17b] ir (CCl_4) 3530 (assoc OH) and 1708 cm^{-1} (C=O). In dilute (0.005 *M*) CCl_4 solution free and intramolecularly associated OH peaks are located at 3600 and 3550 cm^{-1} corresponding to $\Delta\nu$ = 50 cm^{-1}; uv (95% EtOH) series of weak maxima (ε 233–262) in the region 250–270 mμ with a maximum at 291 mμ (ε 265); nmr (CCl_4) δ 7.1–7.5 (5 H, m, aryl CH), 4.18 (1 H, m, CHO), 3.52 (1 H, d, *J* = 5.3 Hz, benzylic CH), 3.33 (1 H, broad, OH, exchanged with D_2O), 2.00 (3 H, s, CH_3CO), and 0.7–1.7 (7 H, m, aliphatic CH). In CH_3OD solution the benzylic CH doublet is located at δ 3.77 with *J* = 7.2 Hz and in C_6D_6 solution the doublet (*J* = 5.1 Hz) is at δ 3.42; mass spectrum, *m/e* (rel intensity) 188 (0.1), 134 (100), 91 (54), and 43 (45).

The same reaction and isolation procedures were employed with variations in the source of the metal enolate to give the results summarized in Table I. The trans lithium enolate **48b** was obtained from the enol acetate **47** and MeLi and the mixture of stereoisomeric lithium enolates containing (nmr analysis[15]) 60% of **49** and 40% of **48b** was obtained by the kinetically controlled reaction of the ketone **46** with $(i\text{-Pr})_2NLi$ as described previously.[15] Aliquots of the crude product from the trans lithium enolate **48b** were analyzed from their nmr spectra in C_6D_6 solution employing the areas under the benzylic CH peaks at δ 3.57 (threo isomer **50a**) and 3.28 (erythro isomer **50b**). After a reaction time of 5 sec, the mixture of aldol products **50** contained 76% of the threo isomer **50a** and after 5 min the mixture contained 78% of the threo isomer **50a**.

The liquid or semisolid chromatographic fractions containing the dialdol products **52** were recrystallized from pentane to separate one of the diastereoisomers of the dialdol **52** as white needles: mp 84–85°;[17b] ir (CCl_4) 3440 (assoc OH) and 1705 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ε 245–300) in the region 250–270 mμ with a maximum at 290 mμ (ε 394); nmr (CCl_4) δ 7.1–7.5 (5 H, m, aryl CH), 3.8–4.5 (2 H, m, CHO), 3.73 (1 H, d, *J* = 9.6 Hz, benzylic CH), 3.37 (2 H, broad, OH, exchanged with D_2O), and 0.7–2.7 (16 H, m, aliphatic CH); mass spectrum, *m/e* (rel intensity) 206 (36), 146 (100), 118 (92), 117 (77), 114 (51), 104 (46), 91 (58), and 43 (39).

Condensation with 2-Methyl-5-*tert*-butylcyclohexanone (53). To a cold (−5 to −25°) solution of 52.5 mmol of MeLi and several milligrams of 2,2′-bipyridyl in 15 ml of DME was added, dropwise and with stirring over 10 min, 5.24 g (24.9 mmol) of the enol acetate **55**. The enolate solution was treated with 25.2 mmol of anhydrous $ZnCl_2$ and the resulting solution was stirred at −3 to 10° for 10 min. Benzaldehyde (2.688 g, 25.3 mmol) was added, dropwise and with stirring during 45 sec, to the cold (−5 to 1°) enolate solution. The resulting reaction mixture was stirred for 3.75 min at 0–1° and then subjected to the usual isolation procedure to leave 7.37 g of crude product as a pale yellow liquid. A CCl_4 solution of an aliquot of this crude reaction product was stirred with D_2O and subjected to nmr analysis to determine the composition of the mixture of aldol products **56** from the relative areas of the benzylic CH peaks. The composition was: 43% axial threo isomer **56a** (δ 5.08); 14% axial erythro isomer **56b** (δ 4.78); 23% equatorial erythro isomer **56c** (δ 4.97); and 21% equatorial threo isomer **56d** (δ 4.72).

On standing 1.090 g (16%) of the crude aldol isomer **56a** separated as prisms, mp 104–109°. Recrystallization (Et_2O–pentane) afforded 580 mg (8.5%) of the pure axial threo isomer **56a** as white plates: mp 113–114°;[17b] ir (CCl_4) 3612 (free OH), 3452 (assoc OH), and 1710 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ε 215 or less) in the region 240–270 mμ with a maximum at 287 mμ (ε 83); mass spectrum *m/e* (rel intensity) 168 (47), 112 (54), 111 (68), 106 (100), 105 (84), 97 (42), 84 (46), 83 (50), 78 (40), 77 (68), 69 (47), 57 (68), and 55 (61); nmr (CCl_4) δ 7.1–7.4 (5 H, m, aryl CH), 5.08 (1 H, d, *J* = 3.5 Hz, benzylic CH), 3.05 (1 H, d, *J* = 3.5 Hz, OH), 2.2–2.6 (2 H, m, CH_2CO), 1.3–2.0 (5 H, m, aliphatic CH), 0.92 (9 H, s, *t*-Bu), and 0.72 (3 H, s, CH_3). In C_6D_6 solution the high-field singlets were shifted to δ 0.98 (CH_3) and 0.78 (*t*-Bu) and the benzylic CH peak was at δ 5.05. Studies of the effect of the lanthanide shift reagent, $Eu(fod)_3$, on the various diastereoisomeric aldols **56** are described subsequently.

The mother liquors from the above crystallization were chromatographed on acid-washed silicic acid[13] with an Et_2O–hexane mixture as the eluent. After removal of 256 mg (5%) of earlier fractions containing the crude unchanged enol acetate **55**, the next fraction contained 987 mg of the crude aldol isomer **56d**, mp 88–93°. Recrystallization (Et_2O–hexane) separated 500 mg (7%) of the pure equatorial threo isomer **56d** as white plates: mp 104.5–105.5°;[17b] ir (CCl_4) 3520 (assoc OH) and 1688 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ε 165–220) in the region 240–270 mμ with a maximum at 289 mμ (ε 47); mass spectrum *m/e* (rel intensity) 168 (57), 106 (44), 105 (60), 84 (68), 83 (60), 77 (100), 57 (74), and 55 (71); nmr (CCl_4) δ 7.1–7.3 (5 H, m, aryl CH), 4.72 (1 H, d, *J* = 2.5 Hz, benzylic CH), 3.91 (1 H, d, *J* = 2.5 Hz, OH, exchanged with D_2O), 2.0–2.5 (2 H, m, CH_2CO), 1.2–2.0 (5 H, m, aliphatic CH), 1.10 (3 H, s, CH_3), and 0.88 (9, H, s, *t*-Bu). In C_6D_6 solution the high-field singlets were shifted to δ 1.00 (CH_3) and 0.65 (*t*-Bu) and the benzylic CH peak was at δ 4.92.

After separation of a fraction (1.111 g, mp 67–74°) containing (tlc) both equatorial isomers **56c** and **56d**, the next fraction, 984 mg of colorless liquid, contained (tlc) a mixture of isomers **56c** and **56b**. Although fractional crystallization was not effective in separating this mixture, use of the subsequently described difference in the rates of retrograde aldol reaction made separation possible. A solution of the mixture of **56b** and **56c** (984 mg) in 5 ml of CCl_4 was stirred at 25° with *ca.* 0.2 ml of aqueous 40% KOH for 5 min at which time nmr analysis indicated practically complete decomposition of the axial aldol isomer **56b**. The CCl_4 solution was washed with aqueous NH_4Cl, dried, concentrated, and chromatographed on silicic acid[13] with an Et_2O–hexane mixture as the eluent. After separation of earlier fractions containing (ir analyses) 138 mg of the ketone **53**, 37 mg of PhCHO, and 57 mg of an unknown component, 192 mg (3%) of the crude equatorial erythro isomer **56c**, mp 96–97°, was collected. Later fractions contained 134 mg of an additional unknown liquid component. Recrystallization of the isomer **56c** from Et_2O–hexane afforded 99 mg of the pure equatorial erythro isomer **56c** as white needles: mp 110–111°;[17b] ir (CCl_4) 3560 (assoc OH) and 1691 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ε 110–203) in the region 240–270 mμ with a maximum at 290 mμ (ε 57); nmr (CCl_4) δ 7.1–7.4 (5 H, m, aryl CH), 4.97 (1 H, d, *J* = 4 Hz, benzylic CH), 2.93 (1 H, d, *J* = 4 Hz, OH), 2.1–2.4 (2 H, m, CH_2CO), 1.1–2.1 (5 H, m, aliphatic CH), 0.98 (3 H, s, CH_3), and 0.90 (9 H, s, *t*-Bu). In C_6D_6 solution the high-field singlets were shifted to δ 0.80 (CH_3) and 0.67 (*t*-Bu) and the benzylic CH peak was at δ 5.17. The mass spectrum has the following peaks: *m/e* (rel intensity) 256 (0.5), 168 (85), 112 (82), 111 (73), 106 (100), 105 (82), 77 (67), 57 (75), and 55 (63).

The next chromatographic fraction (1.172 g of colorless liquid) contained primarily the aldol isomer **56b**. Crystallization from hexane separated 307 mg (5%) of the axial erythro isomer **56b**, mp 90–97°. Recrystallization separated 204 mg (3%) of the pure axial erythro isomer **56b** as white prisms: mp 95–96°;[17b] ir (CCl_4) 3610 (free OH), 3490 (assoc OH), and 1700 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ε 106–191) in the region 240–270 mμ with a maximum at 291 mμ (ε 66); mass spectrum *m/e* (rel intensity) 168 (41), 112 (58), 111 (55), 106 (92), 105 (84), 83 (39), 77 (99), 57 (100), 55 (95), 51 (67), 50 (70), 43 (50), 42 (62), 41 (93), and 39 (67); nmr (CCl_4) δ 7.1–7.4 (5 H, m, aryl CH), 4.78 (1 H, s, benzylic CH), 1.1–2.6 (8 H, m, OH and aliphatic CH), 0.87 (9 H, s, *t*-Bu), and 0.83 (3, H, s, CH_3). In C_6D_6 solution the high field singlets were shifted to δ 0.96 (CH_3) and 0.76 (*t*-Bu) and the benzylic CH peak was at δ 4.87.

The following chromatographic fraction (167 mg) contained a mixture of the axial isomers **56a** and **56b** and the final chromatographic fraction (1.227 g, mp 98–102°) contained the crude axial threo isomer **56a**. After recrystallization of these final fractions a total of 1.273 g (18.7%) of the axial threo isomer **56a**, mp 112–114°, was obtained. The total yield of the various aldol isomers **56** obtained in the various column fractions amounted to 5.733 g (84%).

To examine the effect of reaction time on the proportions of the aldol isomers **56**, a cold (−5 to −15°) solution of the lithium enolate **54**, from 210 mg (1.0 mmol) of enol acetate **55**, 2.05 mmol of MeLi, and 1.5 ml of DME, was treated with 1.5 ml of an Et_2O solution containing 1.05 mmol of $ZnCl_2$. To the resulting cold (−2 to 0°) solution was added, during 2 sec with stirring, 122 mg (1.15 mmol) of PhCHO. Aliquots of the reaction solution were removed after 12 sec and 5 min and subjected to the previously described quenching and nmr analysis. After 12 sec the mixture of aldol isomers contained 54% of **56a**, 16% of **56b**, 18% of **56c**, and 12% of **56d**; after 5 min the composition was 48% of **56a**, 15% of **56b**, 23% of **56c**, and 14% of **56d**. From a comparable reaction where 25% excess MeLi was used, the mixture obtained after 12 sec contained 23% of **56a**, 19% of **56b**, 30% of **56c**, and 28% of **56b**; after 60 min, the same reaction mixture contained 15% of **56a**, 15% of **56b**, 25% of **56c**, and 45% of **56d**.

A synthetic mixture of the aldol isomers **56** (40% of **56a**, 12% of **56b**, 21% of **56c**, and 27% of **56d**) was dissolved in a mixture of 0.4

Table IV. Properties of the Aldol Stereoisomers 56

Isomer	56a, axial Threo	56b, axial Erythro	56c, equatorial Erythro	56d, equatorial Threo
Mp, °C	113–114	95–96	110–111	104.5–105.5
Relative rate of retrograde aldol reaction	Rapid	Rapid	Slow	Slow
CH_3 nmr signal, ($\delta_{CCl_4} - \delta_{PhH}$), Hz	−16 Hz	−6.5 Hz	+11 Hz	+6 Hz
PhCH nmr signal ($\delta_{CCl_4} - \delta_{PhH}$), Hz	+2 Hz	+5 Hz	−12 Hz	−12 Hz
Order of elution from SiO_2	Fourth	Third	Second	First
Ir C=O peak, cm^{-1} (CCl_4 soln)	1709	1707	1691	1687
Ir OH peaks (0.01–0.003 *M* in CCl_4) free OH, cm^{-1}	3616 (s)	3618 (s)	3620 (m)	3617 (w)
Assoc OH, cm^{-1}	3476 (w)	3487 (w)	3583 (s)	3528 (s)
$\Delta\nu$, cm^{-1}	140	131	37	89

ml of CCl_4 and *ca.* 0.1 ml of aqueous 30% KOH. The resulting mixture was shaken at 25° and the composition of the mixture of aldol products was followed by nmr analysis. After 115 min two of the four aldol products had been largely destroyed by retrograde aldol condensation and the remaining mixture of aldol products contained 4% of **56a**, 4% of **56b**, 43% of **56c**, and 50% of **56d**. Thus isomers **56a** and **56b** are assigned configurations with the α-hydroxybenzyl substituents axial, a stereoelectronically favorable conformation for retrograde aldol reaction. A number of physical properties (see Table IV) of the aldol isomers **56** support these stereochemical assignments. In accord with other studies,[39] a change in nmr solvent from CCl_4 to C_6D_6 shifts the equatorial methyl group signals of **56a** and **56b** downfield and the axial methyl group signals of **56c** and **56d** upfield. The same generalization applies to the nmr benzylic CH signals for these isomers.

Infrared studies of the aldol isomers **56** in dilute (0.01–0.003 *M*) CCl_4 (freshly distilled from P_2O_5) solution indicated that intramolecular H bond (—O—H · · · O=C<) is less prevalent in the axial isomers **56a** and **56b**. Each of these cases exhibits a normal C=O stretching frequency (1707–1709 cm^{-1}) and a strong free OH stretching peak in dilute solution. In the equatorial isomers **56c** and **56b** where intramolecular H bonding is geometrically more favorable, the C=O stretching frequencies are lowered (1687–1691 cm^{-1}) and the associated OH stretching peak is strong in dilute solution.

To examine the effect of the lanthanide shift reagent, $Eu(fod)_3$,[40] on the various aldol stereoisomers **56**, CCl_4 solutions (*ca.* 0.3 *M*) of each of the stereoisomers **56** as well as the stereoisomers **37** [with predominantly equatorial PhCH(OH) substituents] were treated with increasing amounts of $Eu(fod)_3$, and the magnitudes of the lanthanide shifts were plotted against the concentration of added $Eu(fod)_3$. The observed lanthanide shifts at molarity ratios, [aldol]/[$Eu(fod)_3$], of 10, determined from these plots, are summarized in Table V.

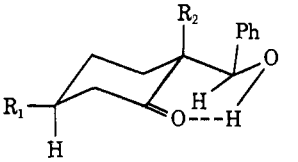
Our assignments of erythro and threo configurations to the pair of axial isomers **56a** and **56b** and the pair of equatorial isomers **56c** and **56d** are tentative since, in these cases, we lack a firm basis for making stereochemical assignments. For the axial pair, the predominance of isomer **56a** in the initial reaction product and the slightly stronger hydrogen bond ($\Delta\nu$ 140 cm^{-1} *vs.* $\Delta\nu$ 131 cm^{-1} for **56b**) have led us to assign the threo configuration to isomer **56a** (mp 113–114°) and the erythro configuration to isomer **56b** (mp 95–96°) since only in the threo isomer **56a** can an intramolecular hydrogen bond (or a metal chelate as in structure **9**) be formed without placing the phenyl substituent over the cyclohexane ring.

In the equatorial pair of isomers **56c** and **56d**, we have compared various physical properties with the models **37a** and **37b** in which the stereochemical assignments are more secure. These comparisons, summarized in Table VI, suggest that the isomer **56c** (mp 110–111°) should be assigned the erythro configuration and isomer **56d** (mp 104.5–105.5°) is then the threo isomer.

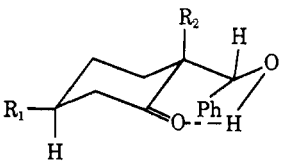
Table V. Lanthanide Induced Shifts in Nmr Signals for the Aldol Isomers **37** and **56** in CCl_4 Solution with a Molarity Ratio, [Aldol]/[$Eu(fod)_3$], of 10

Isomer	Lanthanide induced shift, Hz: PhCH(OH)	α-CH_3 (for **56**) or α-H (for **37**)	CH_2CO
56a (axial threo)	92	85	69
56b (axial erythro)	106	59	66
56c (equatorial erythro)	125	57	75
56d (equatorial threo)	104	47	37
37a (equatorial threo)	105	87	33
37b (equatorial erythro)	100	92	55

Table VI. Comparison of the Properties of the Equatorial Aldol Stereoisomers



threo isomers
37a, $R_1 = R_2 = H$
56d, R_1 = *t*-Bu; $R_2 = CH_3$



erythro isomers
37b, $R_1 = R_2 = H$
56c, R_1 = *t*-Bu; $R_2 = CH_3$

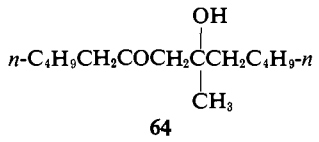
Isomer	$\Delta\nu$ (free assoc OH), cm^{-1}	δ (benzylic CH)	Lanthanide shift ratio $\Delta\delta$(α-CH_3 or α-H)/$\Delta\delta(CH_2CO)$
37a	68	4.68	2.6
56d	89	4.72	1.3
37b	38	5.30	1.7
56c	37	4.97	0.76

Condensation with 2-Heptanone (57). To a cold (1–6°) solution of the enolate **59**, prepared by the addition of 3.86 g (24.8 mmol)

(39) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 159–182.

(40) (a) C. C. Hinckley, M. R. Klotz, and F. Patil, *J. Amer. Chem. Soc.*, **93**, 2417 (1971), and references therein; (b) R. E. Rondeau and R. E. Sievers, *ibid.*, **93**, 1522 (1971).

of the enol acetate **58** (mixture containing *ca.* 75% trans and *ca.* 25% cis stereoisomers) to 15 ml of a DME solution containing 51.7 mmol of MeLi and several milligrams of 2,2'-bipyridyl, was added a solution of 25.2 mmol of $ZnCl_2$ in 36.5 ml of Et_2O. The resulting suspension was stirred at 3° for 10 min and then 2.68 g (25.2 mmol) of PhCHO was added, dropwise and with stirring during 1.5 min while the reaction temperature was maintained at −10 to 15°. The reaction mixture was worked up as usual to leave a crude product (5.848 g of pale yellow liquid) containing (tlc and nmr analysis) approximately equal amounts of the stereoisomeric aldol products **60a** and **60b**. Chromatography on acid-washed silicic acid[13] with Et_2O–hexane mixtures as eluents separated in the early fractions 120 mg (2%) of a colorless liquid believed to be the crude aldol product **64**: ir (CCl_4) 3510 (assoc OH) and 1700 cm^{-1} (C=O); nmr (CCl_4)



64

δ 3.4 (1 H, broad, OH), 2.1–2.6 (4 H, m, CH_2CO), and 0.7–1.9 (23 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 179 (1), 157 (5), 99 (26), 58 (28), 55 (30), 43 (100), 42 (33), 41 (59), and 39 (38). The later fractions contained, in order of elution, 2.175 g (40%) of the liquid erythro aldol **60b**, 340 mg (6%) of a mixture of stereoisomeric aldol products **60a** and **60b**, and 1.834 g (34%) of the liquid threo aldol **60a**. Short-path distillation afforded the erythro aldol **60b** as a colorless liquid: $n^{25}D$ 1.5052;[17b] ir (CCl_4) 3610 (free OH), 3490 (assoc OH), and 1705 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ε 273–318) in the region 240–270 mμ with a maximum at 283 mμ (119); mass spectrum *m/e* (rel intensity) 179 (1), 106 (51), 105 (59), 78 (51), 77 (81), 74 (61), 51 (67), 50 (88), 43 (100), and 41 (77); nmr (CCl_4) δ 7.0–7.3 (5 H, m, aryl CH), 4.66 (1 H, d, J = 6.6 Hz, benzylic CH), 3.42 (1 H broad, OH), 2.5–2.9 (1 H, m, COCH<), and 0.6–1.9 (12 H, m, aliphatic CH with CH_3CO singlet at δ 1.78). In CH_3OD solution the benzylic CH doublet is located at δ 4.77 (J = 7.9 Hz).

Short-path distillation (0.07 mm and 100°) afforded the threo aldol **60a** as a colorless liquid: $n^{25}D$ 1.5065;[17b] ir (CCl_4) 3610 (free OH), 3480 (assoc OH), and 1710 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ε 162–261) in the region 240–270 mμ with a maximum at 282 mμ (ε 114); mass spectrum *m/e* (rel intensity) 202 (0.4), 154 (3), 106 (40), 105 (58), 78 (58), 77 (91), 74 (57), 51 (70), 50 (84), 43 (100), 42 (65), 41 (75), and 39 (74); nmr (CCl_4) δ 7.1–7.4 (5 H, m, aryl CH), 4.55 (1 H, d of d, J = 8.7 and 4.0 Hz, collapsed to doublet, J = 8.7 Hz, with added D_2O, benzylic CH), 3.56 (1 H, d, J = 4.0 Hz, OH, exchanged with D_2O), 2.5–3.0 (1 H, m, COCH<), 2.04 (3 H, s, CH_3CO), and 0.5–1.5 (9 H, m, aliphatic CH). In CH_3OD solution the benzylic CH doublet is at δ 4.70, J = 9.5 Hz.

The same condensation experiment was repeated with the only modification being the addition of PhCHO to the cold (−10°) solution of the lithium enolate **59** and $ZnCl_2$ over a period of only 5 sec. After this addition, aliquots were removed at regular intervals and quenched by partitioning them between cold (0°) aqueous NH_4Cl and Et_2O. The organic solutions were dried, concentrated, and analyzed using the nmr peaks at δ 1.78 (CH_3CO of the erythro isomer **60b**) and 2.04 (CH_3CO of the threo isomer **60a**) to determine the proportions of aldol stereoisomers present. The proportions of isomers after various reaction times were: 19 sec, 55% **60b** and 45% **60a**; 35 sec, 55% **60b** and 45% **60a**; 65 sec, 51% **60b** and 45% **60a**; 125 sec, 50% **60b** and 50% **60a**; 300 sec, 48% **60b** and 52% **60a**. The reaction was essentially complete in a time less than 19 sec when the first aliquot was removed, and the above data indicate that the composition of the aldol product **60a** + **60b** changed relatively little after 19 sec.

Polylithium Compounds. VII.[1,2] The Tetralithium Compound from 1,3-Pentadiyne and Synthesis of Its Organic and Organometallic Derivatives

T. Ling Chwang and Robert West*

Contribution from the Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received November 2, 1972*

Abstract: 1,3-Pentadiyne reacts with excess *n*-butyllithium complexed with TMEDA to form a perlithiated species, C_5Li_4. With water, C_5Li_4 forms three isomers, 1,3-pentadiyne, 1,4-pentadiyne, and 1,2-pentadien-4-yne; with deuterium oxide, the three corresponding perdeuterated isomers are obtained. C_5Li_4 reacts with dimethyl sulfate to give three permethylated isomers, 6,6-dimethyl-2,4-heptadiyne, 4,4-dimethyl-2,5-heptadiyne, and 2,4-dimethyl-2,3-heptadien-5-yne. Quenching C_5Li_4 with either trimethylchlorosilane, ethyldimethylchlorosilane, or *tert*-butyldimethylchlorosilane yields only the sterically controlled products, tetrakis(organosilyl)-1,2-pentadien-4-ynes. Trimethylchlorogermane reacts with C_5Li_4 to give both 1,1,3,5-tetrakis(trimethylgermyl)-1,2-pentadien-4-yne and 1,5,5,5-tetrakis(trimethylgermyl)-1,3-pentadiyne. From infrared spectroscopy, C_5Li_4 is postulated to have mainly a pentatetraene structure, $Li_2C{=}C{=}C{=}C{=}CLi_2$.

Previous papers in this series have reported that many 1-alkynes bearing α-hydrogen atoms are readily polylithiated by alkyllithiums.[2–5] Propyne, for example, reacts with *n*-butyllithium in hexane to give the tetralithium compound C_3Li_4.[4,5] The present paper reports the preparation of another tetralithium compound, C_5Li_4 (**1**), and some of its organic and organometallic derivatives.

A solution of 1,3-pentadiyne (**2**)[6] in *n*-butane reacts with excess *n*-butyllithium complexed with *N,N,N',N'*-tetramethylethylenediamine (TMEDA) to give a viscous dark brown oil. Treatment of this polylithiated material with excess water under acid conditions leads to a

(1) This work was supported by the Air Force Office of Scientific Research (NC), Office of Aerospace Research, USAF, Grant No. AF-AFOSR 70-1904.

(2) A preliminary account of a portion of this work has been reported: R. West and T. L. Chwang, *Chem. Commun.*, 813 (1971).

(3) R. West and G. A. Gornowicz, *J. Amer. Chem. Soc.*, **93**, 1720 (1971), and references cited therein.

(4) R. West, P. A. Carney, and I. C. Mineo, *ibid.*, **87**, 3788 (1965).

(5) R. West and P. C. Jones, *ibid.*, **91**, 6156 (1969).

(6) 1,3-Pentadiene (**2**) was prepared by the method of J. L. H. Allan, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1862 (1955).