

- (4) H. J. Bestmann and R. Zimmermann, *Fortschr. Chem. Forsch.*, **20**, 38 (1971).
 (5) Cf. Y. Shirota, T. Nagai, and N. Tokura, *Tetrahedron*, **23**, 639 (1967).
 (6) Cf. J. F. King, E. G. Lewars, and L. J. Danks, *Can. J. Chem.*, **50**, 866 (1972).
 (7) For a review, see G. Opitz, *Angew. Chem.*, **79**, 161 (1967); see also ref 2b.
 (8) (a) G. Opitz, H. Schempp, and H. Adolph, *Justus Liebigs Ann. Chem.*, **684**, 92 (1965); (b) I. J. Borowitz, *J. Amer. Chem. Soc.*, **86**, 1146 (1964).
 (9) G. Opitz and K. Fischer, *Z. Naturforsch. B*, **18**, 775 (1963).
 (10) R. Fusco, S. Rossi, and S. Maiorana, *Chim. Ind. (Milan)*, **44**, 873 (1962); *Chem. Abstr.* **60**, 13240c (1964).
 (11) Cf. F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).
 (12) W. Davies and J. H. Dick, *J. Chem. Soc.*, 2104 (1931); 483 (1932).
 (13) M. H. Karger and Y. Mazur, *J. Org. Chem.*, **36**, 528 (1971); L. N. Owen and S. P. Whitelaw, *J. Chem. Soc.*, 3723 (1953).
 (14) G. Wittig and U. Schöllkopf, *Org. Syn.*, **40**, 66 (1960).
 (15) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961).
 (16) G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 2342 (1929).
 (17) H. Hoffmann, *Justus Liebigs Ann. Chem.*, **634**, 1 (1960).
 (18) R. Ketcham, D. Jambotkar, and L. Martinelli, *J. Org. Chem.*, **27**, 4666 (1962).
 (19) (a) C. Ziegler and J. M. Sprague, *J. Org. Chem.*, **16**, 621 (1951); (b) J. F. King and D. J. H. Smith, *Can. J. Chem.*, **43**, 1870 (1965).
 (20) R. B. Scott and H. L. McLeod, *J. Org. Chem.*, **21**, 388 (1956).
 (21) F. G. Bordwell, B. M. Pitt, and M. Knell, *J. Amer. Chem. Soc.*, **73**, 5004 (1951).
 (22) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944); S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Amer. Chem. Soc.*, **74**, 1113 (1952).
 (23) R. B. Scott and R. E. Lutz, *J. Org. Chem.*, **19**, 830 (1954).
 (24) D. Seyferth and G. Singh, *J. Amer. Chem. Soc.*, **87**, 4156 (1965).
 (25) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953).
 (26) H. Koch and W. Haaf, *Org. Syn.*, **44**, 1 (1964).
 (27) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **69**, 2548 (1947).
 (28) H. Stetter, M. Schwartz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959).
 (29) H. Stone and H. Schechter, *J. Org. Chem.*, **15**, 491 (1950).
 (30) L. Field and J. W. McFarland, *Org. Syn.*, **36**, 91 (1956).
 (31) G. Opitz, H. Hellmann, and H. W. Schubert, *Justus Liebigs Ann. Chem.*, **623**, 112 (1959).

Alkyl Metal Asymmetric Reduction. VI. Alkyl Phenyl Ketone Reductions by Dialkylzinc Compounds. Some Dynamic and Stereochemical Aspects

Giampaolo Giacomelli, Luciano Lardicci,* and Roberto Santi

Istituto di Chimica Organica, Facoltà di Scienze M.F.N., Università di Pisa, 56100, Pisa, Italy

Received January 8, 1974

The reactivity of organozinc compounds having β -branched alkyl groups toward alkyl phenyl ketones has been investigated; at 86° the dialkylzinc compounds are shown to reduce the carbonyl substrate to the corresponding carbinol, which is the only product formed. On the basis of the results obtained, the reduction process is assumed to involve the formation of a coordinative bond between the ketone and the dialkylzinc compound, followed by a β -hydride transfer from the alkyl group of the organozinc compound to the carbonyl carbon atom in a six-membered cyclic transition state. The eventual occurrence of side reduction processes, like the Meerwein-Ponndorf-Verley reaction, in the experimental conditions was tested too. Finally, the reduction of alkyl phenyl ketones by (+)-bis[(S)-2-methylbutyl]zinc affords (S)-alkylphenylcarbinols. The stereoselectivity of the process is discussed and compared with that encountered in other alkyl metal reductions.

Although the reactivity of the organozinc compounds should correspond in principle to that of their Grignard counterparts, it is generally accepted that organozinc compounds, isolated by distillation, are scarcely reactive toward carbonyl substrates.^{1,2} On the contrary, *in situ* organozinc reagents react rapidly and efficiently with simple carbonyl compounds to give mainly addition products.^{2,3} Concerning the reactivity of *isolated* dialkylzinc compounds, diethylzinc was observed to eliminate ethylene quantitatively in the reaction with benzophenone at 110°, giving ethylzinc diphenyl methoxide.⁴

Therefore, in the course of studies on the reactions of organometallic compounds with functional substrates⁵ and on the alkyl metal asymmetric reductions,^{6,7} we have investigated the actual reactivity of dialkylzinc compounds toward alkyl phenyl ketones and, in this connection, the stereochemistry of their reduction by optically active organozinc compounds.⁷

Results

At relatively high temperatures, dialkylzinc compounds having branched alkyl groups⁷ react with alkyl phenyl ketones; the reactions have been carried out mainly in the absence of solvents at 86.5°. In the experimental conditions adopted, after hydrolysis of the reaction mixtures, secondary carbinols corresponding to the reduction of the carbonyl group are recovered together with the unreacted ketone. No addition product was detected in the reaction of alkyl phenyl ketones with Zn(*i*-Bu)₂ or with bis(2-methylbutyl)zinc, while γ - or δ -branched alkylzinc compounds were observed to yield also tertiary carbinols, although to a

low extent.⁷ The main results we have obtained are summarized in Tables I and II, from inspection of which several general observations can be noted.

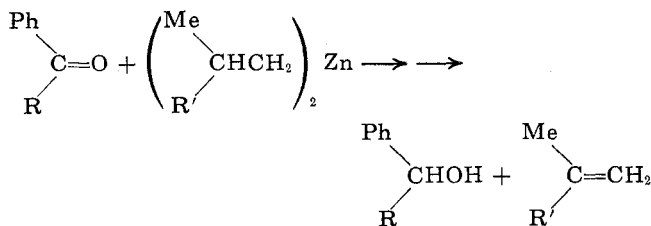
(1) The reaction rate seems to be dependent on the structure and on the nature of the carbonyl substrate; while trifluoromethyl phenyl ketone reacts completely within 20 min at room temperature (runs 11 and 12), the reduction of the alkyl phenyl ketones occurs with conversions higher than 50% only after heating at 86.5° for 5 hr (runs 5–7). Moreover, as the bulk of the alkyl group in the ketone increases, the conversions (after 5 hr) of the reaction decrease from 90–100 to 50–60%.

(2) The reactivity of the organozinc compounds used seems to be nearly comparable; the conversions in the reduction of *tert*-butyl phenyl ketone are, however, slightly lower using Zn(*i*-Bu)₂ than using bis(2-methylbutyl)zinc (runs 9 and 10).

(3) The increase of the concentration of the reagents in toluene solution (runs 14 and 15), as well as the use of an excess of the organozinc compound (run 16), determines higher conversions in the reduction of *tert*-butyl phenyl ketone.

Bis[(S)-2-methylbutyl]zinc is able to accomplish asymmetric reduction of alkyl phenyl ketones (Table III): all the carbinols recovered have the absolute (S) configuration. In agreement with the data obtained in the reduction of the same ketones by (+)-tris[(S)-2-methylbutyl]aluminum,⁸ the stereoselectivity of the reduction is dependent on the structure of the ketone, increasing in the order Me < Et < *t*-Bu < *i*-Pr. Finally, it is to be noted that the reduction of trifluoromethyl phenyl ketone occurs with very low stereo-

Table I
Reduction of Alkyl Phenyl Ketones by
Dialkylzinc Compounds



Run	R	Temp, °C	R'	Conversion % in carbinol ^a after 5 hr
1	Me	86.5	Me	94
2			Et	97
3	Et		Me	75
4			Et	75
5	<i>i</i> -Pr	46.5	Me	9
6		67.5		27
7		86.5		69
8			Et	66
9	<i>t</i> -Bu		Me	62
10			Et	51
11 ^b	CF ₃	25.0	Me	100
12 ^b			Et	100

^a Based on glpc analyses of the crude reaction mixture after hydrolysis. All the values refer to runs carried out at least in duplicate. ^b The reaction is complete within 20 min.

selectivity at 80° in benzene (run 25); the extent of asymmetric reduction is, however, higher at 0° (run 26).

Discussion

In agreement with previous observations,^{4,7} at relatively high temperatures organozinc compounds react effectively with carbonyl substrates (Table I).

Although in principle mixtures of products may be obtained arising from addition, reduction, and enolization processes, the reaction affords essentially the secondary carbinol corresponding to a reduction of the carbonyl group. No addition product has been detected in the reaction mixture in the experimental conditions we have adopted. Moreover, the high conversions of the reduction of alkyl phenyl ketones (Table III) and the recovery of low-boiling material containing 97% of 2-methyl-1-butene in the reduc-

Table II
Reduction of *tert*-Butyl Phenyl Ketone by
Diisobutylzinc at 86.5°

Run	Solvent	Molar ratio Zn(<i>i</i> -Bu) ₂ / ketone	Conversion ^a % after			
			2 hr	5 hr	9 hr	15 hr
13		1	37	62	74	79
14	Toluene ^b	1		41	55	67
15	Toluene ^c	1		26	38	49
16		2	50	76	94	99

^a Based on glpc analyses of the crude reaction mixture after hydrolysis. ^b Molar concentration of Zn(*i*-Bu)₂ 0.93 M. ^c Molar concentration of Zn(*i*-Bu)₂ 0.55 M.

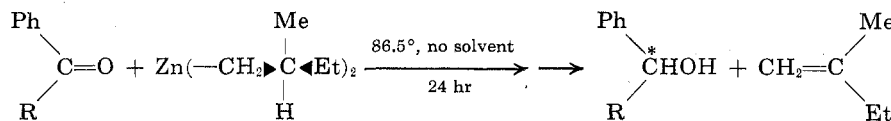
tion of isopropyl phenyl ketone by bis(2-methylbutyl)zinc⁷ seem to exclude also enolization phenomena of relevant extent.⁸

It has already been hypothesized⁴ that the reaction between organozinc compounds and ketones involves a six-center transition state, analogous to that suggested for the reduction of ketones by aluminum alkyls.⁹ The dependence of the reduction rate on the molar ratio Zn(*i*-Bu)₂/ketone (Table II) seems to indicate that the reduction involves a bimolecular process. This hypothesis agrees moreover with the fact that the reaction, carried out in toluene, was found to exhibit second-order kinetics: the plot of *t* against reciprocal concentration of the ketone is in fact a straight line (runs 14 and 15) and the reaction rate depends on the initial concentration of both the reactants in the solution (Table II).

On this basis, also in view of mechanisms already proposed for the reduction of ketones by other organometallic compounds,^{6,9,10} it seems reasonable to assume that the reaction proceeds through the formation of a complex between the ketone and the organozinc compound,^{3b,4} followed by the migration of the β hydrogen from the alkyl group of the dialkylzinc to the carbonyl carbon in a six-center transition state (Scheme I).^{4,7}

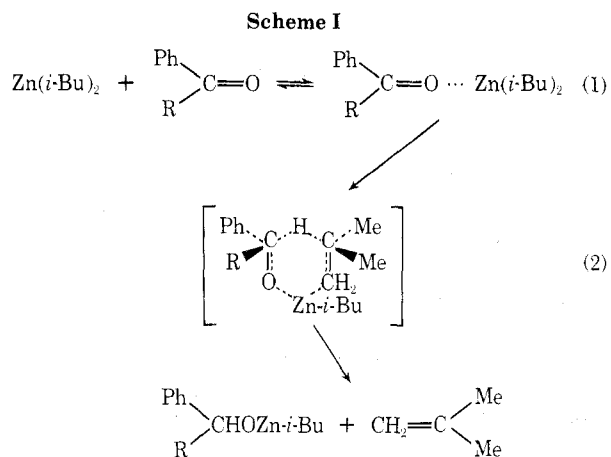
Effectively, when the phenyl alkyl ketone is added to the organozinc compound, the reaction mixture assumes a yellow color which might be attributed to a complex formation;⁴ however, the kinetic results indicate that such a formation occurs either quantitatively or to a very small extent. Actually, although we were unable to determine the exact extent of complexation, the assumption that the

Table III
Asymmetric Reduction of Alkyl Phenyl Ketones by (+)-Bis[(*S*)-2-methylbutyl]zinc^a



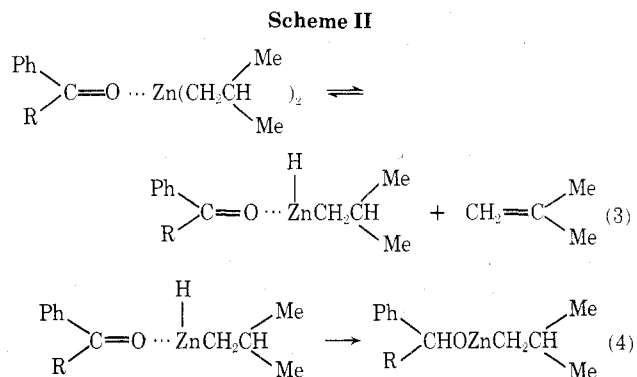
Run	R	Ph(R)C=O registry no.	-S Carbinol							Asymmetric reduction, ^f %
			Conversion ^b %	Chemical purity, ^c %	α ^{25D} , deg, l = 1 (c, ether)	[α] ^{25D}	[α] ^{25D} ^d	Optical purity, ^e %	Registry no.	
17	Me	98-86-2	<i>g</i>	98.3	-0.16 (4.73) ^h	-1.69	-1.72	2.6	1445-91-6	2.6
18			98.2	98.2	-0.15 (4.94) ^h	-1.52	-1.55	2.4		2.4
19	^b Et	93-55-0	78.4	78.6	-0.13 (7.26)	-1.79	-2.28	4.4	613-87-6	4.5
20			79.8	80.0	-0.11 (6.39)	-1.72	-2.15	4.2		4.3
21 ⁱ	<i>i</i> -Pr	611-70-1	89.2	89.3	-0.43 (6.65)	-6.47	-7.24	15.2	34857-28-8	15.5
22 ⁱ			86.7	86.8	-0.52 (8.29)	-6.27	-7.22	15.2		15.5
23	<i>t</i> -Bu	938-16-9	84.4	84.6	-0.33 (10.50)	-3.14	-3.71	10.2	15914-85-9	10.4
24			84.7	85.3	-0.36 (10.94)	-3.29	-3.86	10.6		10.8
25 ^j	CF ₃	434-45-7	~100	~100	+0.18 (neat)	+0.14	0.4	340-06-7		0.4
26 ^k			~100	~100	+0.17 (10.49)	+1.62	5.1			5.2

^a Optical purity 98.2%. ^b Based on glpc analyses of the crude products. ^c Estimated by glpc analyses on redistilled samples, other impurities being the ketone. ^d Corrected for the chemical purity of the carbinol. ^e See Experimental Section. ^f Corrected on the basis of the optical purity of the dialkylzinc. ^g Not determined. High-boiling materials were formed too. ^h l = 2. ⁱ See ref 7. ^j Reaction carried out at 80° in benzene for 1 hr. ^k Reaction carried out at 0° for 1 hr.



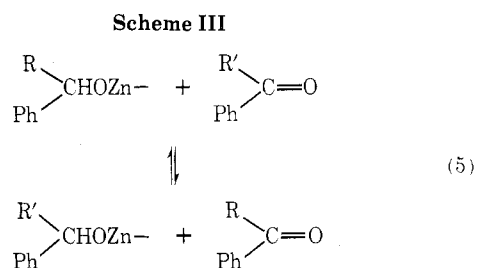
equilibrium constant for complex formation (eq 1) is small seems very reliable.¹¹ Therefore the rate-determining step of the reaction should be reasonably the transfer of the β hydrogen of the alkyl group to the ketone (eq 2).

An alternative mechanistic pathway might be based on the olefin elimination as a consequence of the ketone attack, followed by reduction of the ketone by isobutylzinc hydride^{9,12} (Scheme II). Though the reduction occurs at



relatively high temperatures, this mechanism does not, however, seem probable since dialkylzinc compounds do not form olefin even at temperatures higher than we have adopted.¹³ Moreover, the asymmetric induction observed in the reaction between (+)-bis[(S)-2-methylbutyl]zinc and phenyl alkyl ketones (Table III) is effectively consistent with the hypothesis of a β -hydrogen transfer in a six-membered cyclic transition state (eq 2).^{6a} This transfer should be aided by electron-withdrawing groups attached to the carbonyl carbon atom. The structure and the nature of the ketone seem to have a determining influence on the reactivity of such a substrate toward the organozinc compounds, in relation to both steric and electronic factors. The conversion of the reductions after 5 hr at 86.5° decreases, in fact, as the structure of the phenyl alkyl ketone is changed, in the order Me > Et > *i*-Pr > *t*-Bu; moreover, the reduction of trifluoromethyl phenyl ketone occurs very fast even at 0° (Table I). The decrease of both the steric hindrance to the carbonyl carbon atom and the electron-donor power of the substituent may act to increase the reaction rate, which is, however, strongly enhanced when powerful electron-withdrawing groups are bonded to the carbonyl carbon atom,¹⁴ as in trifluoroacetophenone. The availability of the second alkyl group of the organozinc compound was tested by treating the diisobutylzinc with *tert*-butyl phenyl ketone in the molar ratio 1:2. At 86.5° after 72 hr, the ketone was reduced with a conversion of 54% and this indicates that the reaction of the second alkyl

group occurs at a very reduced rate, analogously to what is observed for the reduction of benzophenone by triisobutylaluminum.⁹ However, in the reaction conditions adopted, the zinc hemialkoxide formed might act as a new reducing agent in a Meerwein–Ponndorf–Verley (MPV) type reaction¹⁵ (Scheme III). Such a reaction should be competing in principle with the alkyl metal reduction, taking into account that the oxygen atom could better stabilize the developing charge on the β -carbon atom and thus favor the hydride transfer from the alkoxide group.¹⁶



As a consequence of this competitive oxidation–reduction mechanism, the optical purity of the carbinols formed in the reduction of the phenyl ketones by (+)-bis[(S)-2-methylbutyl]zinc might change during the reaction time. In fact, when the concentration of the hemialkoxide species in the reaction mixture becomes appreciable the eventual MPV reaction should lead to the racemization of the optically active alkoxide groups formed.¹⁷

Bis[(S)-1-phenyl-2-methylpropoxy]zinc (optical purity 29.4%) was shown to racemize completely if heated at 86.5° for 24 hr in the presence of a stoichiometric amount of the corresponding ketone.¹⁸ In similar conditions bis[(*R,S*)-1-phenylpropoxy]zinc reacts with *tert*-butyl phenyl ketone to yield *tert*-butylphenylcarbinol (48%), as a consequence of a MPV reaction. In order to check if such an oxidation–reduction process occurs even by the zinc hemialkoxide formed by the alkyl metal reduction, isobutyl[(*R,S*)-1-phenyl-2,2-dimethylpropoxy]zinc was heated at 86.5° for 24 hr with the equivalent amount of propiophenone. Upon hydrolysis of the reaction mixture, ethylphenylcarbinol (50% yield) and the corresponding amount of *tert*-butyl phenyl ketone were recovered. Such products are certainly derived from a MPV reaction involving the alkoxide groups (eq 5).

Nevertheless the optical purity of *tert*-butylphenylcarbinol from reduction of the corresponding ketone by (+)-bis[(S)-2-methylbutyl]zinc (runs 23 and 24) does not change with the reaction time (2–48 hr) and consequently with the conversion of the reaction (14–95%). Only when the (S)-2-methylbutylzinc hemialkoxide was heated for an additional 24 hr in the presence of the ketone did the carbinol recovered have a lower optical purity (7.7%) (run 27, Experimental Section).¹⁹

These overall findings and the kinetic results seem to indicate that the MPV reaction is not competing with the transfer of the β hydrogen of the alkyl group bound to the zinc atom, in the experimental conditions adopted for the asymmetric reduction investigations; therefore the stereochemical data reported in Table III are to be considered quite reliable.

In this connection, the first consideration we can make is that the trend of the asymmetric reduction of phenyl alkyl ketones by (+)-bis[(S)-2-methylbutyl]zinc (Table III) is similar to those encountered in the reduction of the same series of ketones by (+)-tris[(S)-2-methylbutyl]aluminum derivatives⁶ or by (S)-2-methylbutylmagnesium halides.¹⁰ Such a trend and the absolute configuration of the carbinol

recovered can be reasonably rationalized on the stereochemical model previously suggested.²⁰

However, the general extent of asymmetric reduction of the phenyl alkyl ketones by (+)-bis[(S)-2-methylbutyl]zinc is lower than that by the corresponding optically active beryllium,^{6a} magnesium,¹⁰ or aluminum derivatives.^{6c} Even if the different reaction conditions adopted in these reactions play an important role, it is our opinion that the different extent of asymmetric reduction encountered with the various alkyl metal compounds^{6,10} is to be connected also with stereoelectronic factors related to the nature of the metal atom and in particular to the Lewis acid strength of the organometallic compound. Such factors should operate to make the cyclic transition states more or less loose, affecting therefore the steric interactions among the groups which are compressed.^{6c}

Experimental Section

General. The alkyl phenyl ketones employed were purified through their semicarbazone derivatives. The dialkylzinc compounds were prepared as described,^{13a} carefully purified by distillation under nitrogen, and stored in sealed capillary-necked glass vials in weighed amounts. All the reactions were carried out in a dry, purified nitrogen atmosphere. Glpc analyses were performed on a C. Erba Fractovap Model GT instrument, with flame ionization detectors, using 200 × 0.30 cm 10% butanediol succinate on 60–80 mesh Chromosorb W columns, operating in the range 130–160°. All rotations were taken on a Schmidt-Haensch polarimeter in 1-dm tubes. The optical purity of the carbinols recovered from the asymmetric reduction experiments were evaluated on the basis of the optical rotations of ether solutions containing both pure carbinol and appropriate amounts of the corresponding ketone.

Reactions of Alkyl Phenyl Ketones with Dialkylzinc Compounds (Runs 1–16). In a typical run *tert*-butyl phenyl ketone (3.0 mmol) was added by a 500- μ l hypodermic syringe to Zn(*i*-Bu)₂ (3.0 mmol) contained in a 25-ml two-necked flask equipped with a Teflon stopper with a rubber septum and a glass stopcock. The reaction vessel was then placed in a thermostatted oil bath, the temperature of which was kept constant at 86.5 ± 0.3°. At intervals samples of the mixture were withdrawn by the hypodermic syringe and hydrolyzed by dilute sulfuric acid. Glpc analyses were performed directly on the ether extracts and showed ketone:carbinol ratios of 1.703, 0.613, 0.351, and 0.266 after 2, 5, 9, and 15 hr, respectively (run 13, Table II).

When 1.78 mmol of Zn(*i*-Bu)₂ was treated at 86.5 ± 0.3° for 72 hr with 3.25 mmol of *tert*-butyl phenyl ketone, glpc analysis on the hydrolyzed reaction mixture showed a ketone:carbinol ratio of 0.852.

Kinetic runs were carried out in an analogous manner using 5 ml of a toluene solution of diisobutylzinc and *tert*-butyl phenyl ketone of known concentrations.

Asymmetric Reductions of Alkyl Phenyl Ketones. A. Runs 17–26. The following procedure (run 24) is representative for all the experiments. To a flame-dried two-neck 100-ml flask, fitted with a magnetic stirrer, a dropping funnel, and a reflux condenser, was added 3.944 g (18.9 mmol) of (+)-bis[(S)-2-methylbutyl]zinc, bp 49° (0.6 mm), $[\alpha]^{25D} +9.91^\circ$ (neat),¹³ followed by 2.777 g (17.1 mmol) of *tert*-butyl phenyl ketone. The flask was then placed for 24 hr in a thermostatted oil bath at 86.5 ± 0.3°. At last the reaction mixture was cooled at 0°, diluted with anhydrous diethyl ether, and cautiously hydrolyzed with dilute sulfuric acid (pH 5). The solvent was removed and the crude product, containing the carbinol and 15.3% of the unchanged ketone, was distilled to yield 2.550 g of (–)-(S)-*tert*-butylphenylcarbinol (85.3% pure), bp 111° (18 mm), α^{25D} (*l* = 1) –0.36° (*c* 10.94, ether).

B. Run 27. As above, 1.411 g (6.8 mmol) of (+)-bis[(S)-2-methylbutyl]zinc, $[\alpha]^{25D} +9.91^\circ$ (neat), was treated with 1.102 g (6.8 mmol) of *tert*-butyl phenyl ketone at 86.5 ± 0.3° for 48 hr. To the reaction mixture 0.739 g (4.5 mmol) of the ketone was then added and the heating was prolonged for an additional 24 hr. The product, recovered after the usual work-up and containing 64.5% of *tert*-butylphenylcarbinol together with unchanged ketone, showed α^{25D} (*l* = 1) –0.19° (*c* 10.58, ether), $[\alpha]^{25D} -1.79^\circ$, $[\alpha]^{25D} -2.77^\circ$ (corrected), optical purity 7.7%.

Reaction between Bis[(S)-1-phenyl-2-methylpropoxy]zinc and Isopropyl Phenyl Ketone. To a 10-ml pentane solution containing 1.4 mmol of diisobutylzinc, cooled at 0°, was added 2.8

mmol of (–)-(S)-isopropylphenylcarbinol, $[\alpha]^{25D} -14.01^\circ$ (*c* 9.37, ether). After 0.5 hr the solvent was removed at reduced pressure, and the solid mass formed was diluted with 3.0 mmol of isopropyl phenyl ketone and heated at 86.5 ± 0.3° for 24 hr. The reaction mixture was then worked up as above; the carbinol recovered (54% pure) showed α^{25D} (*l* = 2) 0.00° (*c* 12.70, ether).

When bis[(S)-1-phenyl-2-methylpropoxy]zinc, prepared as above, was heated at 86.5 ± 0.3° for 24 hr in the absence of the ketone, the carbinol recovered after hydrolysis showed α^{25D} (*l* = 1) –1.20°, $[\alpha]^{25D} -12.97^\circ$ (*c* 9.25, ether).

Reaction between Bis[(R,S)-1-phenylpropoxy]zinc and *tert*-Butyl Phenyl Ketone. Bis[(R,S)-1-phenylpropoxy]zinc (5.1 mmol), prepared from Zn(*i*-Bu)₂ and ethylphenylcarbinol according to the above procedure, was treated with 5.1 mmol of *tert*-butyl phenyl ketone. The mixture was heated at 86.5 ± 0.3° for 24 hr, diluted with diethyl ether, and hydrolyzed to pH 5. Glpc analysis on the ether extracts revealed the presence of ethyl phenyl ketone (16%), ethylphenylcarbinol (51%), *tert*-butyl phenyl ketone (17%), and *tert*-butylphenylcarbinol (17%).

Reaction between Isobutyl[(R,S)-1-phenyl-2,2-dimethylpropoxy]zinc and Propiophenone. To 0.275 g (1.5 mmol) of diisobutylzinc was added 0.249 g (1.5 mmol) of *tert*-butyl phenyl ketone and the mixture was heated at 86.5 ± 0.3° for 48 hr until completion of the reduction reaction. To the isobutyl[(R,S)-1-phenyl-2,3-dimethylpropoxy]zinc thus obtained was successively added 0.251 g (1.5 mmol) of ethyl phenyl ketone and the heating was prolonged for 24 hr. The mixture was hydrolyzed and extracted by ether; glpc analysis on the crude reaction product showed the presence of ethylphenylcarbinol (25%) and of *tert*-butyl phenyl ketone (25%).

Acknowledgment. This work was supported by the Consiglio Nazionale delle Ricerche, Roma.

Registry No.—Zn(*i*-Bu)₂, 1854-19-9; (+)-bis[(S)-2-methylbutyl]zinc, 1731-05-1; bis[(S)-1-phenyl-2-methylpropoxy]zinc, 51849-39-9; bis[(R,S)-1-phenylpropoxy]zinc, 51849-40-2; isobutyl[(R,S)-1-phenyl-2,2-dimethylpropoxy]zinc, 51849-41-3.

References and Notes

- G. E. Coates and K. Wade in "Organometallic Compounds," Vol. 1, 3rd ed, Methuen, London, 1967, pp 130–131.
- B. Marx, E. Henry-Basch, and P. Fréon, *C. R. Acad. Sci., Ser. C*, **264**, 527 (1967).
- (a) P. R. Jones, E. J. Goller, and W. J. Kauffman, *J. Org. Chem.*, **34**, 3566 (1969); (b) P. R. Jones, W. J. Kauffman, and E. J. Goller, *ibid.*, **36**, 186 (1971); (c) P. R. Jones, E. J. Goller, and W. J. Kauffman, *ibid.*, **36**, 3311 (1971).
- G. E. Coates and D. Ridley, *J. Chem. Soc. A*, 1064 (1966).
- (a) L. Lardicci and G. P. Giacomelli, *J. Organometal. Chem.*, **33**, 293 (1971); (b) *Chim. Ind. (Milan)*, **53**, 1152 (1971); (c) G. P. Giacomelli and L. Lardicci, *Chem. Ind. (London)*, 689 (1972); (d) *J. Chem. Soc., Perkin Trans. 2*, 1129 (1973); (e) L. Lardicci, A. M. Caporusso, and G. P. Giacomelli, *J. Organometal. Chem.*, **70**, 333 (1974).
- (a) G. P. Giacomelli, R. Menicagli, and L. Lardicci, *Tetrahedron Lett.*, 4135 (1971); (b) L. Lardicci, G. P. Giacomelli, and R. Menicagli, *ibid.*, 687 (1972); (c) G. P. Giacomelli, R. Menicagli, and L. Lardicci, *J. Org. Chem.*, **38**, 2370 (1973); (d) *J. Org. Chem.*, **39**, 1757 (1974).
- (a) L. Lardicci and G. P. Giacomelli, *J. Chem. Soc., Perkin Trans. 1*, 337 (1974); (b) G. P. Giacomelli, L. Lardicci, and R. Menicagli, communication to the VII Convegno di Chimica Organica, Trieste, Sept 24–27, 1973, Abstracts, p 110.
- In addition it is to be noted that any shift of the resonance lines of benzene solutions of Zn(*i*-Bu)₂ and acetophenone and any new peak were not observed even several days after the preparation of the solutions.
- E. C. Ashby and S. H. Yu, *J. Org. Chem.*, **35**, 1034 (1970).
- J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, pp 177–202.
- Cryoscopic measurements on benzene solutions of diisobutylzinc in the presence of a phenyl alkyl ketone seem to indicate the formation of such a complex, whose concentration in benzene is unfortunately too small to be determined with a certain degree of confidence.
- K. Hess and H. Rheinboldt, *Chem. Ber.*, **54B**, 2043 (1921).
- (a) L. Lardicci and L. Lucarini, *Ann. Chim. (Rome)*, **54**, 1233 (1964); (b) L. Lardicci, L. Lucarini, P. Palagi, and P. Pino, *J. Organometal. Chem.*, **4**, 341 (1965).
- (a) E. T. McBee, O. R. Pierce, and J. F. Higgins, *J. Amer. Chem. Soc.*, **74**, 1736 (1952); (b) R. F. Borch, S. R. Levitan, and F. A. Van-Catledge, *J. Org. Chem.*, **37**, 726 (1972).
- See ref 10, pp 160–177.
- H. Haubenstock and E. B. Davidson, *J. Org. Chem.*, **28**, 2772 (1963).
- The racemization of the optically active alkoxide groups might not occur if the MPV reaction is 100% stereoselective; this eventuality seems in effect very improbable.¹⁵
- After 24 hr at 86.5°, in the absence of the ketone, (–)-(S)-isopropyl-

phenylcarbinol, optical purity 27.2%, was recovered upon hydrolysis.
 (19) A control of the residual optically active 2-methylbutyl group bound to the zinc atom on the stereochemistry of the MPV reaction seems to be excluded.¹⁷ In fact, a similar result was obtained when isobutyl[(S)-1-

phenyl-2,2-dimethylpropoxy]zinc (optical purity 10.2%) was heated at 86.5° for 24 hr with an equivalent amount of *tert*-butyl phenyl ketone; the carbinol recovered was 7.2% optically pure.
 (20) See ref 6c and 7a and references cited therein.

Silane Reductions in Acidic Media. III. Reductions of Aldehydes and Ketones to Alcohols and Alcohol Derivatives. General Syntheses of Alcohols, Symmetrical Ethers, Carboxylate Esters, and Acetamides^{1a}

Michael P. Doyle,^{*1b} Donald J. DeBruyn,^{1c} Stephen J. Donnelly, Dale A. Kooistra,^{1d}
 Abayomi A. Odubela, Charles T. West, and Steven M. Zonnebelt

Department of Chemistry, Hope College, Holland, Michigan 49423

Received April 29, 1974

Aldehydes and ketones are reduced by alkylsilanes to alcohols in aqueous acidic media; both concentrated hydrochloric acid and aqueous sulfuric acid are suitable aqueous acids. A nonreactive solvent such as acetonitrile or ethyl ether is required to minimize ether formation. Symmetrical ethers are formed by silane reductions of aldehydes and ketones in anhydrous acidic solutions under conditions where acid-catalyzed alcohol dehydration does not occur. Carboxylate esters and symmetrical ethers are formed by silane reductions of aldehydes and ketones in carboxylic acid media. Low temperatures and a low concentration of carboxylic acid favors the production of symmetrical ether; ester formation is favored in the reductions of ketones and in reductions using carboxylic acids comparable in acid strengths to formic and acetic acids. In acetonitrile using aqueous sulfuric acid silane reductions of ketones and aryl aldehydes yield *N*-substituted acetamides. The optimum reaction conditions and limitations of these reactions are described. Evidence concerning the mechanism of these interrelated reactions is presented and discussed.

In recent years silanes have received increased interest as reducing agents for organic compounds. Organosilanes are nonpolar liquids or solids, soluble in a wide range of organic solvents, and stable to strong bases and strong acids, except concentrated mineral acids.² Like the boron and aluminum hydrides, silicon hydrides are polarized with a greater electron density at hydrogen than at silicon; hydride transfer from silicon to electropositive carbon is thermodynamically favorable.³ Unlike reductions by the boron and aluminum hydrides which require no external acid catalyst, however, organosilanes require activation of the carbon center by a Lewis acid before hydride transfer can occur.

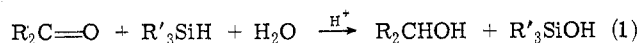
Few reducing agents are as selective as organosilanes toward the carbonyl group of aldehydes and ketones. We have previously reported that reduction of the carbonyl group of aryl aldehydes and ketones to methylene in trifluoroacetic acid occurs without concurrent reduction of the carboxylic acid, carboxylate ester, cyano, nitro, or bromide functional groups.^{1a} Olefins and alcohols are reduced to hydrocarbons in acidic media only if a relatively stable carbenium ion intermediate can be formed.⁴ Terminal arylacetylenes are reduced in low yield to the corresponding alkane by triethylsilane in trifluoroacetic acid;⁵ however, reaction times are long and acid-catalyzed solvation of the carbon-carbon triple bond may have preceded reduction by the silane.

Excluding photochemical reductions involving silanes,⁶ three methods, trichlorosilane-tertiary amine reductions, zinc chloride catalyzed reductions, and reductions in trifluoroacetic acid, have had the widest application for reductions of aldehydes and ketones. Benkeser has used trichlorosilane-tertiary amine combinations to effect reductive silylation of aromatic aldehydes and ketones;⁷ this reaction probably involves the trichlorosilyl anion^{7b} and is, at present, generally applicable only to nonenolizable carbonyl compounds. With trialkylsilanes, however, reactions catalyzed by zinc chloride and leading to either the correspond-

ing symmetrical ether and alkyl silyl ether with aldehydes or to the alkyl silyl ether with ketones appear to have no such limitation for enolizable carbonyl compounds.⁸ Kursanov and coworkers have reported several examples of triethylsilane reductions of aldehydes and ketones in trifluoroacetic acid;^{4a,9} aldehydes are reduced to the corresponding symmetrical ethers and trifluoroacetates while ketones are reduced to trifluoroacetate esters. We wish to report that aldehydes and ketones can be selectively reduced by organosilanes to alcohols, carboxylate esters, symmetrical ethers, or acetamides by suitable changes in the reaction media.

Results

Preparation of Alcohols. Although trifluoroacetate esters, formed by silane reduction of aldehydes and ketones in trifluoroacetic acid,^{4a,9} and alkyl silyl ethers, formed from aldehydes and ketones by silane reduction with zinc chloride catalysis,⁸ are readily hydrolyzed to the corresponding alcohols under relatively mild conditions, these methods offer little advantage over existing reduction methods for the preparation of simple alcohols. In addition, the production of symmetrical ethers from aldehydes in a competitive process further complicates the reduction process. Even though alcohols may be the primary products in these reactions, there has been no report of a direct and general method for the synthesis of alcohols from aldehydes and ketones by silane reduction. We have found, however, that silane reductions can be directed to form alcohols if water is added to the reaction medium (eq 1).



The product composition from the reductions of representative aldehydes and ketones by triethylsilane in aqueous acidic media is given in Table I. (Additional data on benzaldehyde are summarized in supplementary material; see paragraph at end of paper). Triethylsilanol was either