On the Mechanism and Chirality of Enol and Ketophosphonium Salt Formation from the Reactions of α-Halo Ketones or α,α-Dihalo Ketones with Tertiary Phosphines[1]

IRVING J. BOROWITZ,*[2] KENNETH C. KIRBY, JR., PAUL E. RUSEK, AND EDWARD W. R. CASPER

Department of Chemistry, Belfer Graduate School of Science, Yeshiva University, New York, New York 10033

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α-Bromacetophenones, which are further substituted at the α position by bromine or phenyl, react with triphenylphosphine to give isolable enol phosphonium halides. *dl*-Methylpropylphenylphosphine (MPPP) reacts with unhindered α-haloacetophenones to give ketophosphonium salts and with several α,α-dihaloacetophenones or hindered α-haloacetophenones to give enol phosphonium salts. In several cases wherein an α-bromo or α-chloro ketone gives an enol phosphonium salt, the corresponding α-mesyloxy ketone gives the ketophosphonium salt. The reactions of optically active MPPP with α-halopropiophenones, α-chlorobenzyl phenyl ketone, or the corresponding α-mesyloxy ketones, give ketophosphonium salts with *retention* of configuration at phosphorus. The proof of stereochemistry includes base hydrolysis of several of the phosphonium salts to methylpropylphenylphosphine oxide (known to generally occur with inversion at phosphorus) and the Wittig reaction of a derived keto ylide (known to occur with retention at phosphorus). The reaction of α,α-dibromo-α-phenylacetophenone with MPPP to form an enol phosphonium salt occurs with *inversion* of configuration at phosphorus. This is proven by the conversion of the enol phosphonium salt to several products of known chirality in the MPPP series. The basic hydrolysis of enol phosphonium salts is shown to occur by reaction at phosphorus by the use of oxygen-18-labeled sodium hydroxide. The data indicate that ketophosphonium halides are formed by SN2-type displacement of halide ion by a tertiary phosphine. It suggests that enol phosphonium halides are formed *via* enolate halophosphonium intermediates which occur by attack of the phosphine on halogen.

Our previous papers in this series have described the following reactions of triphenylphosphine (TPP) with α-halo ketones. α-Haloacetophenones,[3] α-halopropiophenones,[4] and α-halobenzyl phenyl ketones[5] react with TPP to give α-ketophosphonium salts. α-Bromocyclohexanone gives α- and β-ketophosphonium salts,[4] and α-halo- or α-mesyloxyisobutyrophenone give only β-ketophosphonium salts.[6] The β-ketophosphonium salts occur *via* elimination to the α,β-unsaturated ketone followed by Michael addition of TPP to the β position of the protonated enone.[6] The mechanism of α-ketophosphonium salt formation will be discussed later in this paper.

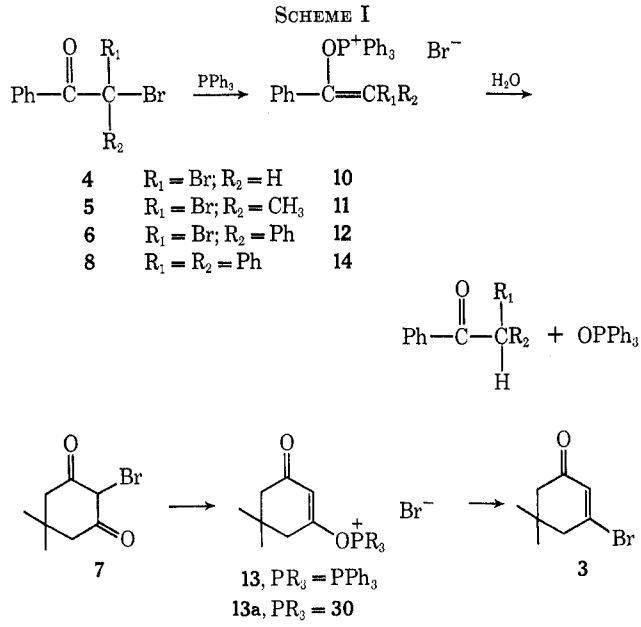
There has also been data on the structural features required for enol phosphonium salt formation. These species have been isolated from the reactions of TPP with α-chloro-α,α-diphenylacetophenone,[7] several α,α-dihalo ketones,[8] and, more recently, from α-bromobenzyl phenyl ketone (**1**) and α-chlorobenzyl phenyl ketone (**2**).[5] They have also been implicated in the reactions of TPP with polyhalo ketones, 2-halo-1,3-diketones,[4,9,10] and in some other cases.[4,10,11]

We now report the isolation of a number of new enol phosphonium salts derived from TPP or from methyl-*n*-propylphenylphosphine (MPPP) and some observations relevant to the pathways involved in their formation. The chirality of the conversions of optically active MPPP to α-keto- or enol phosphonium salts, which allow more rigorous mechanistic conclusions, is also discussed.

Results and Discussion

Enol Triphenylphosphonium Salts.—The reactions of TPP with various α-haloacetophenones and with several other species are presented in Scheme I. It is

SCHEME I



concluded that the presence of a second α-halogen or an α-phenyl group is sufficient to cause enol phosphonium salt formation. 2-Bromodimedone (**7**) reacts rapidly to give 5,5-dimethyl-3-bromocyclohexenone (**3**), presumably *via* **13**.[4]

The acyclic enol phosphonium halides are isolable solids which can be stored for some time under anhydrous conditions. They are readily hydrolyzed by water or aqueous base in solution, however, to give the corresponding ketone and triphenylphosphine oxide (TPPO). We have now shown that the base hydrolysis of enol phosphonium salts proceeds by attack of hy-

(1) This investigation was supported by National Science Foundation Grants No. 5978 and 8676. This is part XI of the series, Organophosphorus Chemistry.

(2) To whom correspondence should be addressed.

(3) (a) I. J. Borowitz and R. Virkhaus, *J. Amer. Chem. Soc.*, **85**, 2183 (1963); (b) I. J. Borowitz and H. Parnes, *J. Org. Chem.*, **32**, 3560 (1967).

(4) I. J. Borowitz, K. Kirby, and R. Virkhaus, *ibid.*, **31**, 4031 (1966).

(5) I. J. Borowitz, P. E. Rusek, and R. Virkhaus, *ibid.*, **34**, 1595 (1969).

(6) I. J. Borowitz, K. Kirby, and P. E. Rusek, *ibid.*, **33**, 3686 (1968).

(7) A. J. Speziale and R. D. Partos, *J. Amer. Chem. Soc.*, **85**, 3312 (1963).

(8) R. D. Partos and A. J. Speziale, *ibid.*, **87**, 5068 (1965).

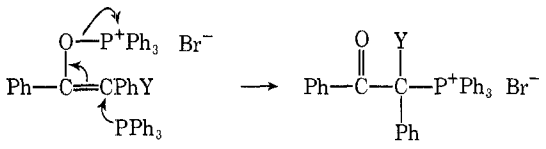
(9) H. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **3**, 737 (1964).

(10) (a) F. Ramirez, K. Tasaka, N. B. Desai, and C. P. Smith, *ibid.*, **33**, 25 (1968); (b) A. J. Speziale and L. R. Smith, *J. Amer. Chem. Soc.*, **84**, 1868 (1962).

(11) D. B. Denney and L. C. Smith, *J. Org. Chem.*, **27**, 3404 (1962).

droxide ion at phosphorus (see below). Treatment of **12** with TPP (1 equiv) at reflux in xylene gave only TPPO, probably formed upon hydrolysis of **12** during work-up. Thus the rearrangement of an enol phosphonium salt to a ketophosphonium salt does not occur in this system. We have previously demonstrated the recovery of the enol phosphonium salt from α-chlorobenzyl phenyl ketone under similar conditions.[5] The rearrangement of an enol to a ketophosphonium salt could have occurred as shown (Scheme II).

SCHEME II



Y = Br, Cl, Ph, H

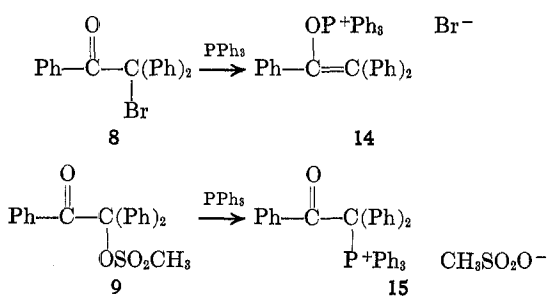
Proton nmr spectral data for **10–14** are given in the Experimental Section. Although previous workers[7,8,10] have reported ^{31}P nmr data for several enol phosphonium salts, we were not able to get satisfactory spectra for our compounds.[12]

The geometric isomerism of the enol phosphonium salts formed remains an unsolved problem which is currently under investigation.

The reaction of dibromo ketones, such as **4**, to give the enol phosphonium bromide, followed by hydrolysis to α-bromoacetophenone, constitutes a mild method for the conversion of α,α-dibromo ketones to α-monobromo ketones. Several examples are given in the Experimental Section.

The Reactions of α-Mesyloxy Ketones with Phosphines.—In contrast to **8**, which gives the enol phosphonium salt **14**, the α-mesyloxy ketone **9** reacts with TPP to give the α-ketophosphonium mesylate **15** (Scheme III). The keto- and enol phosphonium salts **14**

SCHEME III

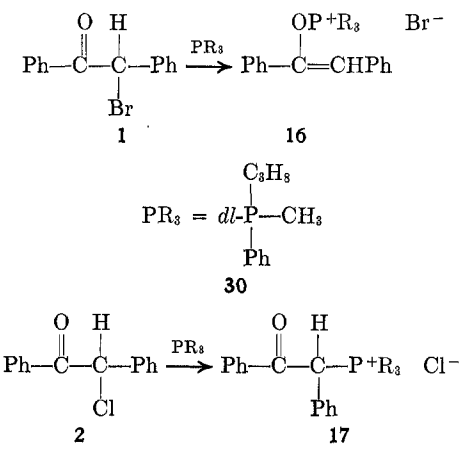


and **15** were shown to be stable to further reaction with TPP (see Experimental Section); *i.e.*, they do not interconvert.

This tendency of an α-mesyloxy ketone to give the α-ketophosphonium salt, even when the corresponding α-bromo or α-chloro ketone gives an enol phosphonium salt, has been previously noted and discussed by us in the benzyl phenyl ketone series.[5] It appears to be generally true that primary and secondary α-mesyloxy ketones react with TPP to form ketophosphonium mesylates. These reaction systems avoid the complications found with some α-halo ketones: dehalogenation and enol phosphonium salt formation. Tertiary α-mesyloxy ketones give either α-ketophosphonium salts, as does **9**, or β-ketophosphonium salts, as does the isobutyrophenone system. Further examples of the reactions of α-mesyloxy ketones (for general syntheses, see ref 24) with TPP and with *dl*-methyl-*n*-propylphenylphosphine (MPPP) are given in Table I.

The Reactions of *dl*-MPPP with α-Halo Ketones.—The recent and elegant work of Mislow and Horner has provided a simplified route to optically active phosphines such as MPPP **30**.[13] Since we wished to utilize **30** in determining the chirality of the formation of enol and ketophosphonium salts, we initially investigated its reactions with various α-halo ketones and related species. The data thus obtained are summarized in Tables I and II. We conclude that **30** behaves reasonably similarly to TPP so that stereochemical and mechanistic results obtained with the former phosphine will probably be valid for the latter. The major difference noted is the tendency for **30** to form enol phosphonium salts in some cases where TPP does not. Thus α-bromoisobutyrophenone forms an enol phosphonium salt with **30** while it undergoes dehydrobromination with TPP as already mentioned. The reactions of α-bromobenzyl phenyl ketone **1** and α-chlorobenzyl phenyl ketone **2** with TPP have been previously shown by us to give mixtures in which enol phosphonium salts predominate at 25° in nonpolar solvents and ketophosphonium salts predominate at higher temperatures and in polar solvents.[5] The reactions with **30** are much cleaner since **1** gives only the enol phosphonium bromide **16** while **2** gives only the ketophosphonium chloride **17** (Scheme IV).

SCHEME IV



Finally, the reactions of 2,4,6-trimethyl-α-bromoacetophenone **18** and 2,4,6-trimethyl-α-mesyloxyacetophenone **19** are of interest. While the α-bromo compound leads rapidly to the enol phosphonium bromide **20**, the α-mesyloxy ketone **19** reacts much more slowly to give the ketophosphonium mesylate **21** (Scheme V). These results are in contrast to the reaction of **18** with TPP which is rather complex.[14]

(12) Attempted ^{31}P nmr spectra at 23.8 MHz were done by Mr. Hara of Jeolco on a C-60 H nmr spectrometer at Upsala College.

(13) (a) O. Korpiun, R. A. Lewis, J. Chickos, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4842 (1968); (b) J. P. Casey, R. A. Lewis, and K. Mislow, *ibid.*, **91**, 2789 (1969); (c) L. Horner and W. D. Balzer, *Tetrahedron Lett.*, 1157 (1965).

(14) R. F. Hudson and G. Salvadori, *Helv. Chim. Acta*, **49**, 96 (1966).

Table I

Conversion of α-Mesyloxy Ketones to Ketophosphonium Salts

α-Mesyloxy ketone	Reaction conditions	Yield, %	Registry no.[a]	Properties of ketophosphonium salts: Mp, °C	Ir (CH_2Cl_2), μ	Nmr ($CDCl_3$), τ
α-Mesyloxyacetophenone	TPP, glyme, reflux, 3 days	82	26709-81-9	147–148.5	5.95 (C=O), 8.20–8.50 ($CH_3SO_2O^-$)	7.40 (s, 3, OSO_2CH_3), 4.0 (d, 2, J_{PH} = 13 Hz), 1.60–2.50 (m,, 20, phenyl H)
α-Mesyloxypropiophenone	As above	80	26709-82-0	149–151.5	5.95 (C=O), 8.1–8.5 ($CH_3SO_2O^-$)	8.1 (q, 3, CH_3, J_{PH} = 19 Hz, J_{HH} = 5.0 Hz), 7.20 (s, 3, OSO_2CH_3), 1.70–2.90 (m, 21, phenyl, methine H)
α-Mesyloxycyclohexanone	TPP, glyme, reflux, 20 days	72	14724-77-7	212.5–214	*b*	*b*
α-Mesyloxycyclododecanone	As above	87[d]	26709-84-2	Oil[c]	5.85, 8.1–8.7	
α-Mesyloxyacetophenone	MPPP	100[e]				
2,4,6-Trimethylacetophenone	MPPP, $CDCl_3$, 45°, 7 days	100[e]	26709-85-3	163–165	5.9, 7.9–8.6	7.95 (s, 3, *p*-CH_3), 7.8 (s, 6, *o*-CH_3), 7.4–9.3 (m, 7, propyl H), 7.55 (d, 3, PCH_3, J_{PH} = 13.5 Hz), 7.45 (s, 3, OSO_2CH_3), 5.1 (d, 1, J_{PH} = 13.5 Hz), 1.7–3.3 (m, 7, aryl H)
α-Mesyloxybenzyl phenyl ketone	MPPP, CH_3NO_2, reflux, 4 hr	76	26697-52-9	130–135	5.9, 8.2–8.4	8.9 (t, 3), 7.6 (d, PCH_3, J_{PH} = 14 Hz), 7.5 (d, J_{PH} = 14 Hz), 7.2 (s, 3), 6.7–8.6 (m, 4), 1.7–2.8 (m, 16, phenyl, methine H)

[a] The salt. [b] Previously reported.[24] [c] Purified as keto ylide. [d] Crude. [e] Nmr tube experiment.

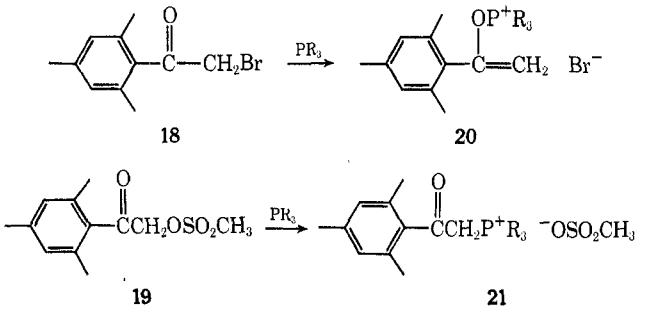
Table II

Reactions of Methyl-*n*-propylphenylphosphine with α-Halo Ketones

α-Halo ketone	Reaction time[a]	Yields, % Enol phos	Yields, % Ketophos	Registry no.	Spectral data: Ir (CH_2Cl_2), μ	Nmr ($CDCl_3$),[b] τ
α-Bromoacetophenone	5 min	0	100[d]	26709-86-4[j]		1.6–2.9 (m, 10), 4.25 (d, 2, J_{PH} = 14 Hz)
α-Bromopropiophenone	30 min, glyme	0	94[e]	26697-53-0[j]	5.98 (C=O), 8.25, 11.0	1.3–2.7 (m, 10), 3.0–3.8 (m, 1), 8.0–8.5 (m, 3, CCH_3)
α-Chloropropiophenone	24 hr[c]	0	100[d]	26709-87-5[j]	5.95, 8.3, 11.1	
	48 hr, glyme	0	65–76[e]			
α-Bromoisobutyrophenone	6 days	100[d,f]		26709-88-6[k]	3.2–3.7, 6.9, 8.6–9.4, 9.5–10.1, 10.6–11.6	1.6–2.7 (m, 10), 8.05 (d, 3, vinyl CH_3, J_{PH} = 2.1 Hz), 8.29 (d, 3, vinyl CH_3, J_{PH} = 3.0 Hz)
α-Chloroisobutyrophenone	30 days	0[d]	0[d]			
α-Bromobenzyl phenyl ketone	5 min	100[d]	0[d]	26709-89-7[k]	3.2–3.6, 7.0, 9.0, 9.9–10.4	1.7–2.8 (m, 15), 3.25 (d, 1, vinyl H, J_{PH} = 2.8 Hz)
α-Chlorobenzyl phenyl ketone	30 min	0	100[d] 77[e]	26709-90-0[j]	6.0 (C=O), 6.3, 6.95, 7.4–7.9, 8.0–8.5, 9.0, 9.9, 10.0, 14.5	1.25–3.0 (m, 16, phenyl, methine H), 7.35 (d, PCH_3, J_{PH} = 14 Hz), 7.60 (d, PCH_3, J_{PH} = 14 Hz)
2,4,6-Trimethyl-α-bromoacetophenone	10 min	100[d,g]	0	26709-91-1[k]		1.7–3.2 (m, 7), 4.2 (s, 1, vinyl H), 5.2 (s, 1, vinyl H), 7.7 (s, 3, *p*-CH_3), 7.85 (s, 6, *o*-CH_3)
α,α-Dibromoacetophenone	5 min	100[h]	0	26709-92-2[k]	3.2–3.7, 7.0, 9.0–9.7, 9.8–10.3	1.6–2.7 (m, 10), 3.3 (d, 1, vinyl H, J_{PH} = 1.9 Hz)
α,α-Dibromopropiophenone	5 min	100	0	26709-93-3[k]	3.2–3.7, 7.0, 9.8–10.3	1.7–2.7 (m, 10), 7.47 (d, vinyl CH_3, J_{PH} = 2 Hz), 7.72 (d, vinyl H, J_{PH} = 3.2 Hz); ratio of 1:2 (vinyl isomers)
α,α-Dibromobenzyl phenyl ketone	5 min	100[d] 87[e,i]	0	26709-94-4[k]	3.2–3.5, 8.2, 8.9, 9.2–9.6, 10.3–10.6	1.65–3.1 (m, 15), 7.25 (d, PCH_3, J_{PH} = 14 Hz), 7.7 (d, PCH_3, J_{PH} = 14 Hz)

[a] All reactions at 25° in $CDCl_3$ under nitrogen unless otherwise indicated. [b] All compounds also gave τ *ca.* 7.1 (d, 3, PCH_3, J_{PH} = 14 Hz), 6.5–9.2 (m, 7, propyl H), except as noted. [c] In nitromethane. [d] Estimated yield from nmr spectrum. [e] Isolated yield. [f] Characterized by hydrolysis with D_2O to give methyl-*n*-propylphenylphosphine oxide (100%) and α-deuterioisobutyrophenone (100%). [g] Characterized by hydrolysis with H_2O (5 min) to **35** (100%) and 2,4,6-trimethylacetophenone (100%). [h] Characterized by hydrolysis to α-bromoacetophenone and **35** (100% each). [i] Characterized by hydrolysis to α-bromobenzyl phenyl ketone (98%) and **35** (96%). [j] Keto. [k] Enol.

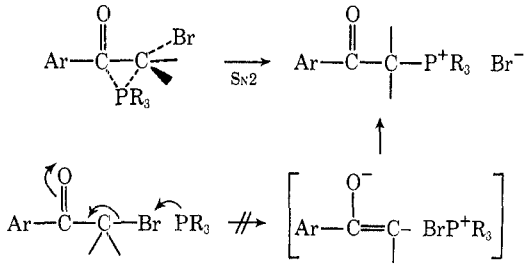
SCHEME V



In contrast to the result for TPP, α-bromodimedone **7** reacts with **30** to rapidly give the enol phosphonium bromide **13a**, which is then slowly converted to the bromo-enone **3** (see Scheme I). This may reflect the fact that methyl-*n*-propylphenylphosphine oxide is a poorer leaving group than is triphenylphosphine oxide.

We have recently argued that different mechanistic pathways are involved for the formation of keto- and enol phosphonium salts.[5] Our previous arguments are enforced by the data presented in Tables I and II. The accumulated data strongly suggest that α-ketophosphonium salts are formed by an SN2 type of displacement of halide or mesylate ion by the tricovalent phosphine. We have shown that kinetic studies of the formation of α-ketophosphonium bromides from aryl-substituted α-bromoacetophenones[3b] and α-bromopropiophenones[15] give Hammett ρ values of +0.44 and +0.67, respectively. These values are compatible with simple displacement of halide ion in these systems as found for solvolysis of α-bromoacetophenones by pyridine[15,16a] or ethanol.[16b] They are in contrast to ρ 2.6 found for attack on halogen of α,α-dihaloamides by TPP.[16c] Such data are not compelling, however, since we cannot be sure that our previously postulated mechanism involving attack on halogen (Scheme VI) would

SCHEME VI



give a ρ value that is quite different. We had argued that such a scheme should lead to a larger positive ρ value. Recent work, however, on the base-catalyzed bromination of aryl-substituted acetophenones, wherein formation of the respective enolates is rate determining, has given a ρ value of only +0.75 at 30°.[17a] We therefore felt that further evidence was needed and we have proven the SN2 pathway by the use of optically active **30** (see below.)

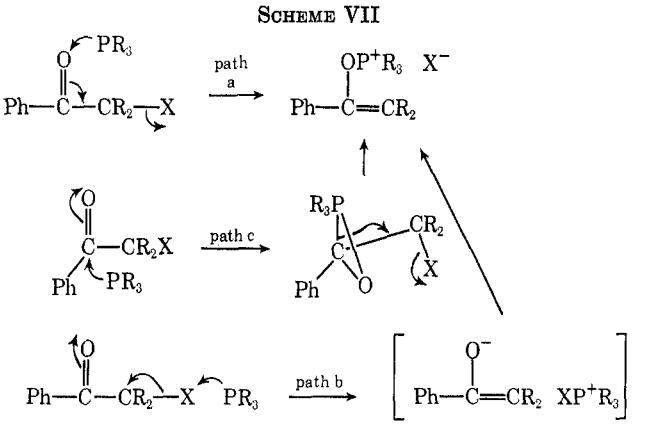
(15) H. Parnes, Ph.D. Thesis, Yeshiva University, 1970.

(16) (a) R. G. Pearson, S. H. Langer, F. V. Williams, and W. J. McGuire, *J. Amer. Chem. Soc.*, **74**, 5130 (1952); (b) D. J. Pasto, K. Garves, and M. P. Serve, *J. Org. Chem.*, **32**, 774 (1967); (c) A. J. Speziale and L. J. Taylor, *ibid.*, **31**, 2450 (1966).

(17) (a) D. N. Nanda, P. L. Nayak, and M. K. Rout, *Indian J. Chem.*, **7**, 469 (1969); (b) S. Trippett, *J. Chem. Soc.*, 2337 (1962).

The suggested mechanisms for the formation of enol phosphonium salts include: (path a) direct attack on carbonyl oxygen by the phosphine,[10a,17b] (path b) attack on halogen by phosphine to give an enolate halophosphonium ion pair which then interacts to give O-phosphorylation,[5,7,8,10b] and (path c) addition of the phosphine to carbonyl carbon (or across the carbonyl) to give an intermediate which rearranges to the O-phosphonium salt (Scheme VII). Other possibilities are eliminated

SCHEME VII



by our observations that keto- and enol phosphonium halides are not interconvertible.

We believe that path c is eliminated by our observations. Thus the fact that **18**, known to have a hindered carbonyl,[16a] reacts rapidly with MPPP to give **20** cannot be explained by path c. Also, if path c were operative, α-bromocyclohexanone **22** and α-chlorocyclohexanone **23** should readily react to give enol phosphonium salts. This would be expected since addition to cyclohexyl carbonyl is most facile.[18] This expectation is borne out in the reactions of **22** and **23** with triethyl phosphite (TEP) to give enol phosphates readily at about the same reaction rate.[19] These reactions are best explained by rate-determining carbonyl addition.[19,20] The reactions of **22** and **23** with TPP occur slowly, however, in anhydrous media to give mixtures of α- and β-ketophosphonium salts.[4,21] Finally the fact that highly substituted halo ketones, such as **3**, **6**, or **8**, react rapidly with either TPP or MPPP to give enol phosphonium salts does not seem to be compatible with path c. We suggest that direct addition of a "soft" phosphine to the "hard" oxygen of carbonyl (path a)[22] is not a likely process. Path a would require that the postulated SN2′-type of reaction should be much better for **18** than for **19**, for example, while **19** prefers to react more slowly by an SN2 process. It is not obvious why this should be so.

Path b, in our opinion, best explains all of the observations involving enol phosphonium salt formation. Attack on "soft" halogen by a "soft" phosphine should be enhanced by further substitution at the α carbon by bulky and electron-withdrawing groups such as phenyl or bromine. Such substitution has the effect of (a)

(18) H. C. Brown and K. Ichikawa, *Tetrahedron Lett.*, 221 (1957).

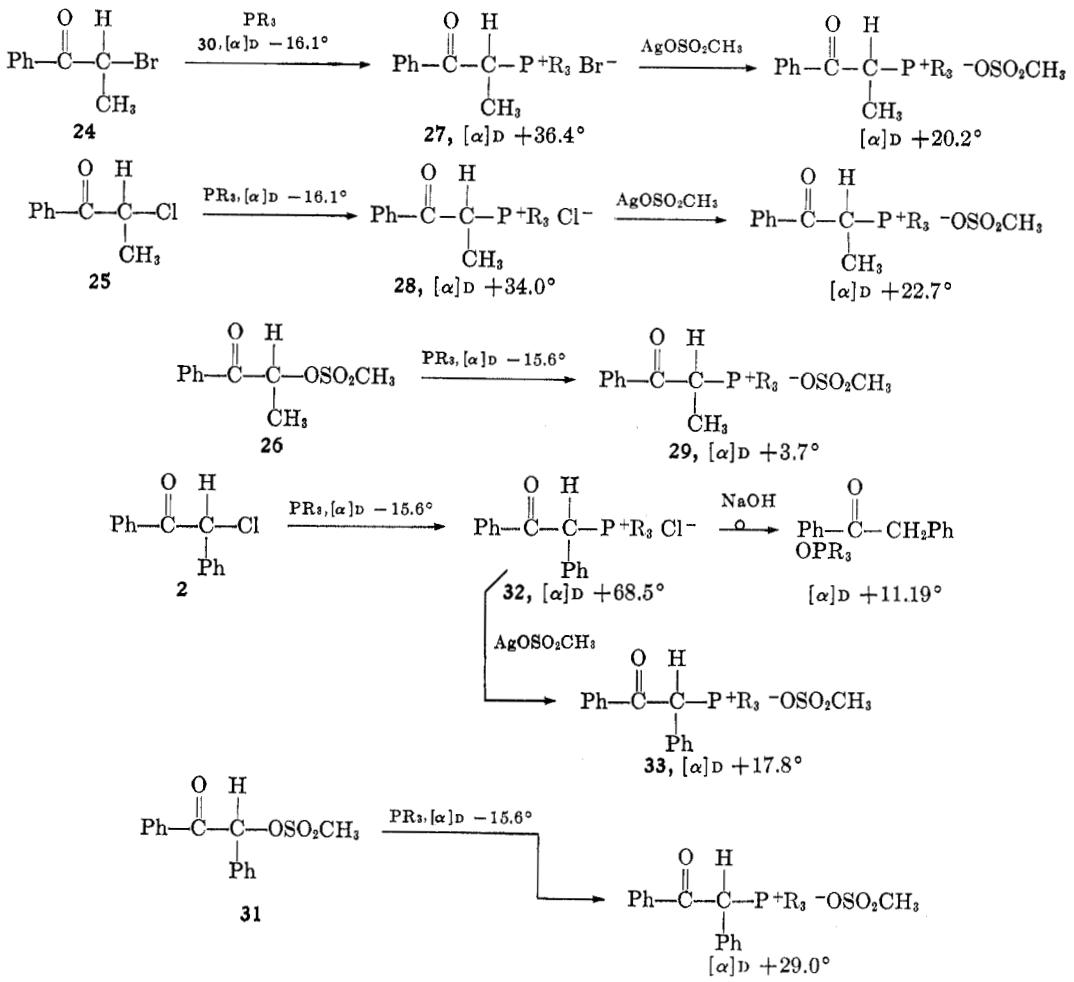
(19) I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

(20) P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, **21**, 1961 (1965).

(21) P. A. Chopard and R. F. Hudson, *J. Chem. Soc. B*, 1089 (1966).

(22) (a) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967); (b) B. Saville, *Angew. Chem., Int. Ed. Engl.*, **6**, 928 (1967).

SCHEME VIII



retarding the normal SN2 displacement of halide ion because of steric reasons, and (b) stabilizing the real or incipient enolate ion which results from removal of positive halogen by the phosphine. Indeed we have found that the acid-catalyzed debromination of α-bromobenzyl phenyl ketone **1** with TPP is much more rapid than the corresponding debromination of α-bromoacetophenone.[23] These debromination reactions involve attack on bromine by TPP.[15,23]

The tendency for MPPP to form enol phosphonium salts more readily than does TPP may indicate that the "halophilicity" (reactivity of a nucleophile toward halogen) of a given phosphine is enhanced by electron-donating groups as much or more than its "carbophilicity" or reactivity toward carbon. Studies on the relative halophilicities of various tricovalent phosphines and other "soft" nucleophiles are in progress.

Finally, path b would be expected to be operative for bromine > chlorine ≫ mesyloxy groups which is the observed order of ease of enol phosphonium salt formation. This relative reaction order is also found for the conversion of α-halo ketones and α-mesyloxy ketones to ketones by diphenylphosphine. These reactions have been postulated to involve attack on halogen or mesyloxy oxygen by the phosphorus.[24]

In order to further probe the mechanisms of keto- and enol phosphonium salt formation, we determined the chirality of their formation with optically active MPPP **30**.

The Chirality of Ketophosphonium Salt Formation.—The reactions of α-substituted propiophenones and benzyl phenyl ketones with (−)-(*R*)-**30** are given in Scheme VIII and the Experimental Section. All of the reactions led to optically active phosphonium salts with the same (+) sign of rotation. Although the chirality of the phosphonium salts was not directly determinable, we argued that all of these reactions must be occurring with retention of configuration at phosphorus since this would be the result of SN2 displacement of the leaving group by the phosphine and since the SN2 pathway is the only tenable one for the α-mesyloxy ketones at least.

This assignment of retention at phosphorus, and confirmation of the SN2 pathway for the formation of all of the keto phosphonium salts, was verified as shown in Scheme IX. Hydrolysis of the (−)-phosphonium bromide **27** from (+)-(*S*)-**30** with aqueous base gave (−)-methyl-*n*-propylphenylphosphine oxide **35**, an overall *inversion* of configuration from **30** to **35**.[25] Since base hydrolysis of most phosphonium salts is known to occur with *inversion* of configuration at phosphorus,[26] our result indicates that the conversion of **30** to the phosphonium salt **27** must occur with retention at phosphorus.

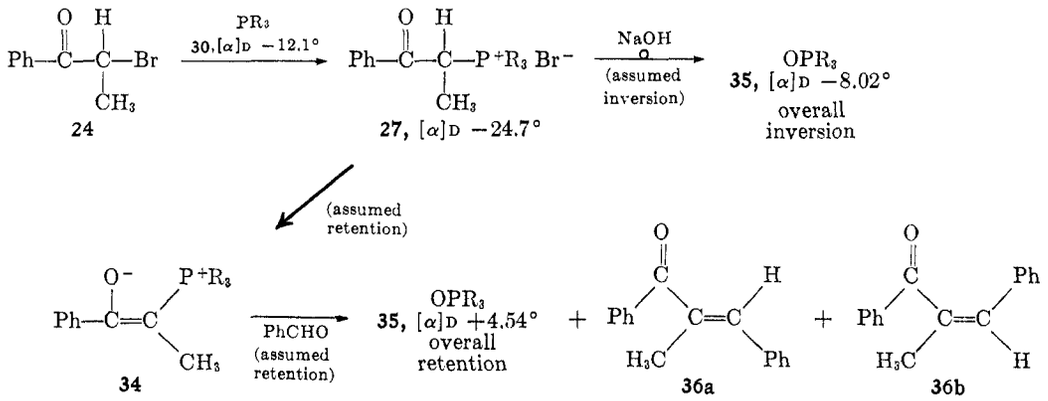
(23) Performed by Dr. E. Lord, Yeshiva University.

(24) I. J. Borowitz, K. Kirby, P. E. Rusek, and E. Lord, *J. Org. Chem.*, **34**, 2687 (1969).

(25) The conversion of (−)-**30** to (−)-**35** involves retention of configuration at phosphorus: L. Horner, *Pure Appl. Chem.*, **9**, 225 (1964).

(26) W. E. McEwen, *et al.*, *J. Amer. Chem. Soc.*, **81**, 3806 (1959). See ref 41 for more recent confirmatory evidence.

SCHEME IX



Finally, the keto ylide **34**, derived from **27**, gave a Wittig reaction with benzaldehyde to give the methylchalcone **36a–36b** in 93.5:6.5 ratio (see Experimental Section) and (+)-**35**, an overall *retention* of configuration from **30** to **35**. Since both conversion of a phosphonium salt to the corresponding ylide and the Wittig reaction of ylides are known to occur with *retention* of configuration at phosphorus,[27a] again the conversion of **30** to **27** must occur with *retention* at phosphorus. In a similar hydrolysis the phosphonium chloride **32** from **2** was shown to form with retention on phosphorus (Scheme VIII).

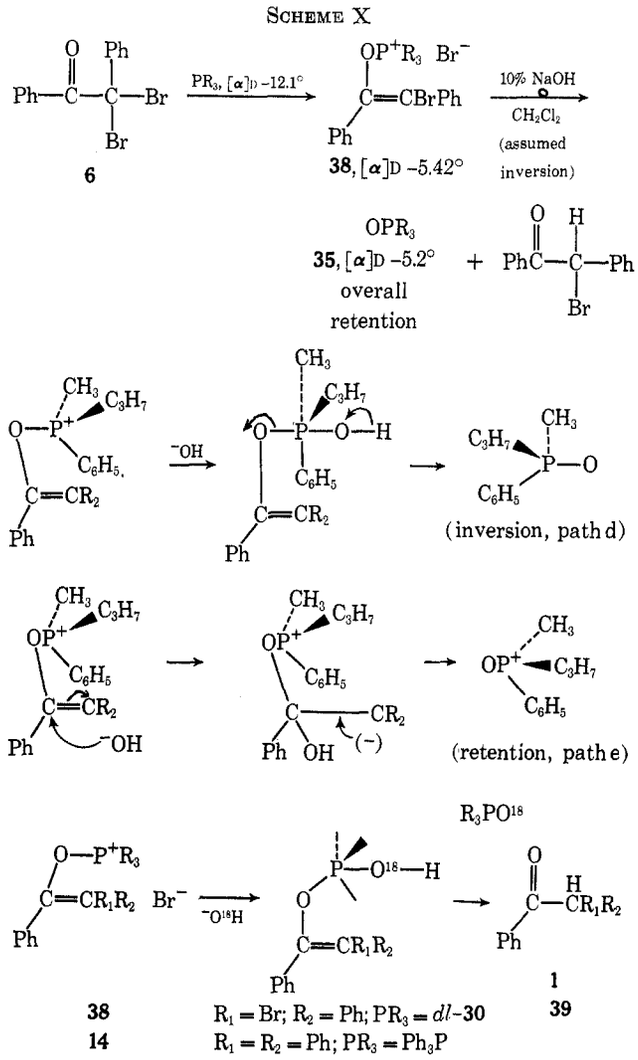
Some racemization is evident in some of these reactions. Whether this racemization involves pseudorotation of pentacovalent phosphorus intermediates or is otherwise mechanistically significant is not clear from our available data.[27b]

The Chirality of Enol Phosphonium Salt Formation.—It was anticipated that differentiation between paths a and b (Scheme VII) for enol phosphonium salt formation should be possible *via* the use of optically active **30**. Thus direct attack on carbonyl oxygen (path a) should give enol phosphonium salts with *retention* of configuration on phosphorus. Path b should involve *inversion* at phosphorus, perhaps accompanied by some racemization depending upon the extent of involvement of pentacovalent intermediates and resultant pseudorotation. This approach has been previously utilized.[28]

The reaction of (−)-**30** with **6** to give (−)-enol phosphonium salt **38** is shown in Scheme X. Since the chirality of **38** could not be determined directly, several reactions of **38** involving predictable chiral changes were undertaken to convert it to **35**. Base hydrolysis of **38** gave (−)-**35**, an overall *retention* of configuration from (−)-**30**. The cause of the partial loss of optical activity noted is not clear. The maximum value should be **35**, $[\alpha]D$ −12.4°, from **30**, $[\alpha]D$ −12.1°.[13b] Since the hydrolysis of **38** probably occurs by inversion at phosphorus (path d, Scheme X), the observed overall retention from **30** to **35** requires that **30** is converted to **38** with *inversion* of configuration. The base hydrolysis of enol phosphonium salts could conceivably occur by Michael addition to carbon of **38**, as in path e,[29] resulting in retention of configuration. We proved that path d, and not path e, is involved in the base hydrolysis of enol phosphonium salts as follows. The reaction of *dl*-**38** with $NaO^{14}H$, prepared from H_2O^{18} containing 10 atom % excess oxygen-18, gave *dl*-**35** which contained all of the excess oxygen-18 as determined by mass spectrometry. A similar result was obtained in the base hydrolysis of the enol triphenylphosphonium salt **14**.

The mass spectral results for **35** are based on a comparison of the relative intensity of the peaks at 139,

SCHEME X



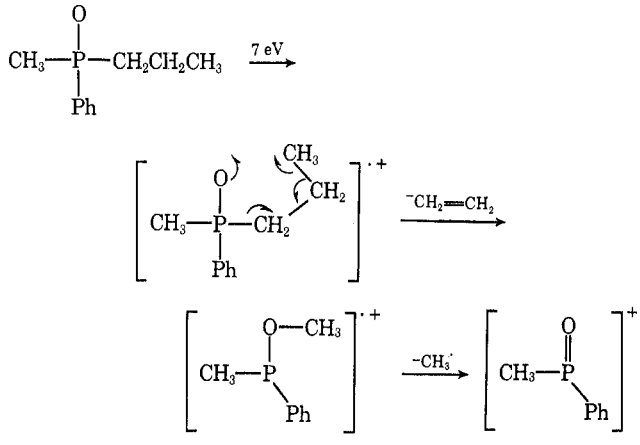
(27) (a) L. Horner and H. Winkler, *Tetrahedron Lett.*, 3265 (1964); (b) the reaction of **26** with **30** is slow, therefore giving racemization of **30** during the reaction.

(28) (a) M. J. Gallagher and I. D. Jenkins in "Topics in Sterochemistry," Vol. 3, N. L. Allinger and E. L. Eliel, Ed., Wiley, New York, N. Y., 1968. (b) For the reactions of chloral with (−)-**30**, see D. B. Denney and N. E. Gershman, *Tetrahedron Lett.*, 3899 (1965). See also D. B. Denney and N. G. Adin, *ibid.*, 2569 (1966).

(29) Such enol phosphonium salts do give Michael additions of halide ion upon pyrolysis.[7,8]

154, and 182 for O^{16}-**35** with those of the O^{18}-enriched **35** as well as the corresponding peaks at M + 2 (see Experimental Section). These peaks presumably arise as shown in Scheme XI.

SCHEME XI



The introduction of oxygen-18 into the phosphine oxide **35** derived from **38** supports the assumption of inversion of configuration in the hydrolysis. Thus enol phosphonium salts are formed with inversion of configuration at phosphorus, a fact which eliminates direct attack on carbonyl oxygen by phosphorus but which can be explained by path b (Scheme VII) involving attack at halogen by phosphorus.

Attempts to displace the phosphine moiety from (−)-**38** and thus regenerate **30** with tributylphosphine or tris(dimethylamino)phosphine were unsuccessful.

The reaction of (−)-**30** with bromodimedone gave *dl*-**35**. Since racemization could have occurred for a variety of reasons no mechanistic conclusions can yet be made for this case.[30]

Further Data on Enol Phosphonium Salt Formation.—As additional evidence that the formation of enol phosphonium salts may involve displacement on halogen by a tertiary phosphine, we have trapped the initial product, bromotriphenylphosphonium ion, resulting from such attack, as follows. The reaction of **8** with TPP and aniline (1 equiv) in acetonitrile rapidly gives the debrominated ketone **39** and anilinotriphenylphosphonium bromide **40** (88%). We have formed **40** from the reaction of bromotriphenylphosphonium bromide and aniline. The enol phosphonium bromide **14**, upon treatment with aniline in acetonitrile for a longer time period, gives only 4% yield of **40** (Scheme XII). Thus, at least in the presence of aniline, TPP removes positive bromine from **8**.[31] Our results confirm the previous work in this area by Speziale,[8,10b] Hoffmann,[9] Denney,[11,28] and our group.[3-6,24]

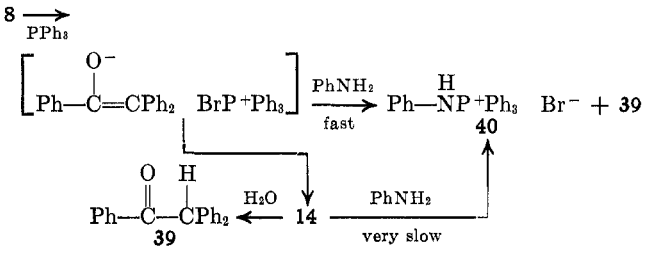
Experimental Section[32]

All of the solvents used were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride.

(30) Thus hydrogen bromide could have racemized optically active **35** had it formed. See ref 28 and D. B. Denney, A. K. Tsolis, and K. Mislow, *J. Amer. Chem. Soc.*, **86**, 4486 (1964).

(31) We realize that the presence of aniline could change another mechanism to one involving attack on bromine. Alcohols do this, in some halo ketone cases, presumably *via* hydrogen bonding to carbonyl oxygen.[23] In the aniline reactions, the active agent could be aniline hydrobromide. Further work on this point is in progress.

SCHEME XII



Reactions were conducted under an atmosphere of prepurified nitrogen. Organic solutions were dried over magnesium sulfate. α,α-Dibromoacetophenone, α-bromobenzyl phenyl ketone, α-chlorobenzyl phenyl ketone, 2,4,6-trimethyl-α-mesyloxyacetophenone, α-chloropropiophenone, and α-bromopropiophenone were prepared as previously described[4,19] or purchased. Most reactions with triphenylphosphine (TPP) were run to completion as shown by the absence of a mercuric chloride adduct.[4]

α,α-Dibromopropiophenone was prepared in 89% yield from the bromination of propiophenone, bp 179–181° (60 mm) [lit.[33] bp 180° (64 mm)]. α,α-Dibromobenzyl phenyl ketone was synthesized from benzyl phenyl ketone in 70% yield, mp 110–112° (lit.[34] mp 110–112°). α-Bromo-α,α-diphenylacetophenone was synthesized from the bromination of diphenylacetophenone in benzene at reflux for 5 hr, mp 85–95° (88% yield); recrystallized from heptane, mp 95.5–97.5° (lit.[35] mp 97–98°). Diphenylacetophenone was synthesized from the reaction of α-chlorobenzyl phenyl ketone with benzene and aluminum chloride in 87% yield, yellow needles from 95% ethanol, mp 135–137.5° (lit.[36] mp 135–137°).

Formation of Enol Triphenylphosphonium Bromide from α-Bromo-α,α-diphenylacetophenone.—A mixture of α-bromo-α,α-diphenylacetophenone (3.51 g, 0.010 mol) and TPP (2.62 g, 0.01 mol) at 25° in glyme (50 ml) for 22 hr ($HgCl_2$ test then negative) gave the enol triphenylphosphonium bromide **14**: 5.35 g, 0.0087 mol, 87%; mp 165–167°; ir ($CHCl_3$) 3.40 (s), 6.30 (m), 6.90 (s), 8.10 (m), 8.53 (m), 8.90 (s) 9.10, 9.35, 10.0, 10.31, and 11.15 μ (m), similar to literature values for corresponding chloride.[7,8]

Anal. Calcd for $C_{38}H_{30}BrOP$: C, 74.39; H, 4.93; Br, 13.02; P, 5.05. Found: C, 74.10; H, 5.05; Br, 12.92; P, 5.04.

Treatment of **14** with H_2O–CH_3OH (1:3) rapidly gave α,α-diphenylacetophenone (identical by tlc using 5% EtOAc–C_6H_6 with a genuine sample). Treatment of **14** (1.29 g, 0.0021 mol) with TPP (1.10 g, 0.0042 mol) in acetonitrile (10 ml) at reflux for 18 hr led to recovery of **14** (1.05 g, 0.0017 mol, 82%), mmp 169–172° with a genuine sample of **14** (mp 171–173°).

Reaction of α,α-Dibromoacetophenone with Triphenylphosphine.—A mixture of α,α-dibromoacetophenone (10.0 g, 0.0360 mol) and TPP (9.45 g, 0.0360 mol) was stirred at 25° in glyme (45 ml) for 10 days. The mixture was then slurried in additional glyme (20 ml) and the solid was quickly filtered off on a sintered glass funnel dried at 200°. After quickly transferring the solid to a predried flask, the remainder of the glyme was removed with a vacuum pump. Purification of the solid by repeated slurrying in dry glyme, followed by filtration and drying, gave a white solid, 1-phenyl-1-triphenyloxyphosphonium-2-bromoethylene bromide (**10**): 14.2 g, 0.0261 mol, 72.5%; ir (CH_2Cl_2) 3.6, 3.8,

(32) Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on Beckman IR-8 and Perkin-Elmer 257 infrared spectrophotometers. Gas chromatograms were recorded on Varian Aerograph A-700 and Hy-Fi III gas chromatographs. Nmr spectra were recorded on a Varian A-60A spectrometer with TMS as an internal standard. Melting points were taken on Mel-Temp and Thomas–Hoover "Uni-Melt" apparatus. They as well as boiling points are uncorrected. Optical rotations were taken on a Bendix-NPL automatic polarimeter. Thin layer chromatography plates were prepared with Brinkmann silica gel HF_{254} and were developed in various solutions as indicated. Mass spectra were done on Hitachi RMU-6 mass spectrometers at Einstein Medical School, N. Y., and Columbia University.

(33) R. Levine and J. R. Stephens, *J. Amer. Chem. Soc.*, **72**, 1642 (1950).

(34) H. Limpricht and H. Schwanert, *Justus Liebigs Ann. Chem.*, **155**, 59 (1850).

(35) C. C. Stevens and J. J. DeYoung, *J. Amer. Chem. Soc.*, **76**, 718 (1954); R. Anschutz and P. Forster, *Justus Liebigs Ann. Chem.*, **368**, 89 (1909).

(36) H. Rinderknecht, *J. Amer. Chem. Soc.*, **73**, 5770 (1951).

6.35, 7.0, 9.7, 9.9, and 10.1 μ; nmr ($CDCl_3$) τ 2.0–2.9 (m, 20, aryl H) and 3.5 (d, 1, vinyl H, $J_{^{31}PH}$ = 1.8 Hz).

Reaction of α,α-Dibromobenzyl Phenyl Ketone with Triphenylphosphine.—Similar reaction of TPP (15.0 g, 0.0575 mol), α,α-dibromobenzyl phenyl ketone (20.4 g, 0.0575 mol) in dry glyme (125 ml) for 24 hr gave 1-phenyl-1-triphenyloxyphosphonium-2-phenyl-2-bromoethylene bromide (**12**): 30.0 g, 0.0487 mol, 84%; ir (CH_2Cl_2) 3.6, 3.8, 6.3, 9.0, 9.6, 9.9, and 10.1 μ; nmr ($CDCl_3$) τ 2.0–3.0 (m, 25, aryl H).

Anal. Calcd for $C_{32}H_{25}OPBr_2$: C, 62.30; H, 4.05. Found: C, 62.59; H, 4.26.

Treatment of **12** with TPP (1 equiv) in xylene at reflux for 17 hr gave recovered **12** which was hydrolyzed to triphenylphosphine oxide and α-bromobenzyl phenyl ketone and no other products.

***In Situ* Formation of α-Mesyloxy-α,α-diphenylacetophenone and Reaction with Triphenylphosphine.**—α-Bromo-α,α-diphenylacetophenone (3.51 g, 0.010 mol) and silver mesylate (2.03 g, 0.010 mol) at 25° for 1 hr in benzene (35 ml) gave crude **9**. Silver bromide was removed by filtration, triphenylphosphine (2.62 g, 0.010 mol) was added to the residual solution, and the mixture was stirred overnight at 25° to give a precipitate which was filtered and dried to give crude α,α-diphenylphenacyltriphenylphosphonium mesylate (**15**, 4.21 g, 0.0067 mol, 67%). Crude **15** was recrystallized twice from ethyl acetate–methanol and once from diethyl ether–methylene chloride to give **15**, mp 184–186°; ir and nmr spectra of the crude salt and analytical sample were very similar: ir ($CHCl_3$) 3.30 (m), 3.37 (m), 5.99 (s), 6.25 (m), 6.73 (m), 6.95 (m), 8.32 (s), 9.00 (m), 9.12 (m), 9.61 (s), and 10.01 μ (m); nmr ($CDCl_2$) τ 7.30 (s, 3, methyl H) and 2.60 (m, 30, aromatic H).

Anal. Calcd for $C_{39}H_{33}O_4PS$: C, 74.52; H, 5.25; P, 4.94. Found: C, 74.61; H, 5.10; P, 4.83.

Several attempts to isolate α-mesyloxy-α,α-diphenylacetophenone resulted in unstable tars and oils in addition to yields from 80 to 100% of silver bromide.

The Stability of α,α-Diphenylphenacyltriphenylphosphonium Mesylate (15).—A mixture of **15** (0.520 g, 0.0083 mol) and triphenylphosphine (0.218 g, 0.0083 mol) was heated at reflux overnight in acetonitrile (10 ml), solvent was removed *in vacuo*, and benzene was added to the residual oil which solidified upon scratching to give **15** (0.390 g, 0.0062 mol, 75% recovery), tlc (50% CH_3OH–C_6H_6) one spot with same R_f value as for genuine **15**.

Reactions of α-Mesyloxy Ketones with Triphenylphosphine and with *dl*-Methyl-*n*-propylphenylphosphine.—The synthesis of α-mesyloxy ketones has been described.[24] In a general procedure, TPP and the appropriate α-mesyloxy ketone were heated at reflux in dry glyme for several days. The corresponding ketophosphonium mesylates were usually isolated by filtration after the reaction mixture was cooled. Spectral and other data are given in Table I.

α-Triphenylphosphoniumcyclododecanone mesylate (41), thus synthesized, was difficult to isolate. Crude **41** (1.8 g, 0.0034 mol) in $CHCl_3$ (100 ml) was stirred with 1 *N* NaOH (50 ml, 0.050 mol) for 1 hr. Removal of the $CHCl_3$ layer, drying, and evaporation *in vacuo* gave an oil which was crystallized from petroleum ether to give the keto ylide **42** (0.69 g, 0.0016 mol, 42%): mp 190–192°; ir (CH_2Cl_2) 6.75 μ (C=O); nmr ($CDCl_3$) τ 2.0–2.9 (m, 15, aryl H) and 7.8–8.7 (m, 20 alicyclic H).

Anal. Calcd for $C_{30}H_{35}OP$: C, 81.41; H, 7.97. Found: C, 81.68; H, 7.85.

2,4,6-Trimethylphenacyl methyl-*n*-propylphenylphosphonium mesylate (21) was isolated from $CDCl_3$.

Anal. Calcd for $C_{22}H_{31}O_4PS$: C, 62.53; H, 7.39. Found: C, 62.22; H, 7.33.

The Reaction of α-Halo Ketones with *dl*-Methyl-*n*-propylphenylphosphine.—In a general procedure, the α-halo ketone and *dl*-MPPP **30** (0.001–0.006 mol each) were mixed with $CDCl_3$ (1 ml) in a 5-mm nmr tube. The nmr spectrum of the resulting mixture was recorded after *ca.* 5 min (for α-bromo ketones) to *ca.* 24 hr (for α-chloro ketones). In some cases larger scale reactions were run. The reaction conditions and spectral data are given in Table II. Similar conditions were used for reactions with TPP.

α-Methylphenacyl methyl-*n*-propylphenylphosphonium bromide (from α-bromopropiophenone and **30**) was recrystallized from Et_2O–CH_2Cl_2, mp 164–165°.

Anal. Calcd for $C_{19}H_{24}BrOP$: C, 60.17; H, 6.38; Br, 21.07; P, 8.19. Found: C, 60.40; H, 6.52; Br, 21.22; P, 8.19.

α-Methylphenacyl methyl-*n*-propylphenylphosphonium chloride (from α-chloropropiophenone and **30**) was crystallized from glyme, mp 137–139.5°.

Anal. Calcd for $C_{19}H_{24}OPCl$: C, 68.36; H, 6.94. Found: C, 68.16; H, 7.11.

α-Phenylphenacyl methyl-*n*-propylphenylphosphonium chloride (from α-chlorobenzyl phenyl ketone and **30**) was crystallized from glyme.

Anal. Calcd for $C_{24}H_{26}OPCl$: C, 72.63; H, 6.60. Found: C, 72.33; H, 6.48.

Enol phosphonium bromide 38 (from **30** and **6**) gave the following analysis.

Anal. Calcd for $C_{24}H_{25}Br_2OP$: C, 55.41; H, 4.84; ionic Br, 15.36. Found: C, 54.38; H, 4.89; ionic Br, 15.01. The analysis could not be improved.

Reaction of 2-Bromodimedone (7) with Methylphenyl-*n*-propylphosphine.—Methylphenyl-*n*-propylphosphine (0.302 g, 0.00182 mol) in $CDCl_3$ (1 ml) was added to an nmr tube containing **7** (0.398 g, 0.00182 mol). After 5 min, the reaction gave enol phosphonium salt (100% by nmr): nmr ($CDCl_3$) τ 1.65–2.3 (m, 5, phenyl H), 4.32 (m, 1, vinyl H), 6.75 (d, 3, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), 7.2 (s, 2, C_4H), 7.7 (s, 2, C_6H), 8.95 (s, 6, methyl H), and 6.2–9.2 (m, 7, propyl H). After 10 days 5,5-dimethyl-3-bromocyclohex-2-enone (**3**) (100% by nmr) [nmr ($CDCl_3$) τ 3.72 (t, 1, vinyl, J = 1 Hz)[4]] and methylphenyl-*n*-propylphosphine oxide (100% by nmr) were present. The decrease of τ 4.32 (vinyl H of **13a**) and increase of τ 3.72 (vinyl H of **3**) could be followed with time. Similar reaction of **7** with TPP immediately gave **3** (nmr) and no evidence of **13**.

Methyldiphenylphosphine was synthesized from chlorodiphenylphosphine and methylmagnesium bromide in 63% yield: bp 136–143° (0.25 mm) (lit.[37] bp 248°); nmr ($CDCl_3$) τ 2.71 (m, 10, phenyl H) and 8.42 (d, 3, CH_3, $J_{^{31}PH}$ = 3.5 Hz).

Treatment of methyldiphenylphosphine with *n*-propyl iodide in benzene at reflux for 3 days gave **methyl-*n*-propyldiphenylphosphonium bromide (43)** in 62–89% yield, mp 210–213.5°.

Methyl-*n*-propylphenylphosphine Oxide (*dl*-35).—A mixture of silver oxide (0.275 mol) and **43** (64 g, 0.20 mol) in distilled water (1500 ml) was heated on a steam bath for 1 hr with stirring and was cooled. After filtration of solids, the filtrate was extracted with $CHCl_3$ (five 100-ml portions). The organic solution was dried, evaporated *in vacuo*, and distilled to give *dl*-**35** (25.0 g, 0.137 mol, 69%): bp 110° (0.025 mm) [lit.[38] bp 180° (13 mm)]; nmr ($CDCl_3$) τ 2.0–2.4, 2.45–2.65 (m, 5, aryl H), 8.4 (d, 2, PCH_3, $J_{^{31}PH}$ = 13.5 Hz), 7.85–8.85 (m, 4), and 9.05 (t, 3, CCH_3).

Methylphenyl-*n*-propylphosphine.—Trichlorosilane (26.8 g, 0.20 mol) was added dropwise to a well-stirred solution of phenylmethylpropylphosphine oxide (25.0 g, 0.137 mol) and triethylamine (20.24 g, 0.200 mol) in dry benzene (200 ml, distilled from $LiAlH_4$). After stirring for 24 hr, sodium hydroxide (30%) was slowly added until solution occurred. The benzene layer was separated, dried, and evaporated *in vacuo*, to leave an oil which was distilled to give methylphenyl-*n*-propylphosphine (13.0 g, 0.08 mol, 58%): bp 97–98° (0.5 mm); nmr ($CDCl_3$) τ 2.3–3.0 (m, 5, phenyl H), 8.45 (d, 3, methyl, $J_{^{31}PH}$ = 3.0 Hz), and 8.2–9.3 (m, 7, propyl H).

Optically active methyl-*n*-propylphenylphosphine oxide (35) was synthesized by known procedures[13a] to give (+)-**35**: bp 108–110° (0.05 mm); $[\alpha]^{20}D$ +17.2° (*c* 0.535, CH_3OH); nmr ($CDCl_3$) τ 2.0–2.9 (m, 5, phenyl H), 8.39 (d, 3, methyl H, $J_{^{31}PH}$ = 13.5 Hz), 9.1 (t, 3, CH_2CH_3), and 7.8–9.1 (m, 4, methylene H).

(−)-Methylphenyl-*n*-propylphosphine.[13c]—To a cooled mixture of (+)-**35** [8.1 g, 0.0445 mol, $[\alpha]^{20}D$ +17.2° (*c* 0.535, methanol)] and triethylamine (222 g, 2.18 mol) in C_6H_6 (500 ml), trichlorosilane (162 g, 1.2 mol) was added dropwise. After a reflux period of 1 hr, 30% aqueous sodium hydroxide was added dropwise until complete solution occurred. The aqueous layer was extracted with chloroform (four 400-ml portions) and dried, and the solvent was removed *in vacuo*, to leave an oil which was distilled to give methylphenyl-*n*-propylphosphine (5.2 g, 0.032 mol, 71%): $[\alpha]^{20}D$ −16.1° (*c* 0.790, methanol); bp 47–48° (0.5 mm); nmr ($CDCl_3$) τ 2.0–2.8 (m, 5, phenyl H), 8.8 (d, 3, methyl H, $J_{^{31}PCH_3}$ = 3.5 Hz), and 8.2–9.2 (m, 7, propyl H).

Reaction of (−)-Methylphenyl-*n*-propylphosphine with α-Chloropropiophenone.—α-Chloropropiophenone (0.76 g, 0.0045

(37) A. Michaelis and E. Kohler, *Chem. Ber.*, **10**, 807 (1877).

(38) J. Meisenheimer and R. Lichtenstadt, *Justus Liebigs Ann. Chem.*, **449**, 213 (1926).

mol) and (−)-methylphenyl-*n*-propylphosphine [0.75 g, 0.0045 mol, $[\alpha]^{20}D$ −16.1° (*c* 0.790, CH_3OH)] were stirred in dry glyme (5 ml, distilled from $LiAlH_4$) for 24 hr. A white solid was filtered off and dried *in vacuo* to give α-methylphenacylmethylphenyl-*n*-propylphosphonium chloride (**28**): 1.25 g, 0.0035 mol, 84%; mp 136–139°; ir (CH_2Cl_2) 3.2–3.7, 5.95 (C=O), 8.3, and 11.1 μ; nmr ($CDCl_3$) τ 1.3–2.9 (m, 10, phenyl H), 2.95–3.4 (m, 1, methine H), 8.29 (d, $J_{^{31}PH}$ = 7.5 Hz), 8.60 (d, $J_{^{31}PH}$ = 7.5 Hz), 7.45 (d, 3, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), 6.6–7.3, 8.0–8.7 (m, 4), and 8.95 (m, 3, propyl CH_3); $[\alpha]^{20}D$ +34° (*c* 0.682, CH_2Cl_2).

Anal. Calcd for $C_{19}H_{24}OPCl$: C, 68.36; H, 6.94. Found: C, 68.37; H, 6.95.

Reaction of (+)-28 with Silver Mesylate.—α-Methylphenacyl methylphenyl-*n*-propylphosphonium chloride [0.50 g, 0.0015 mol, $[\alpha]^{20}D$ +34° (*c* 0.682, CH_2Cl_2)] in acetonitrile (25 ml) was added to a solution of silver mesylate (0.30 g, 0.00148 mol) in acetonitrile (5 ml). The silver chloride was filtered off and the solvent removed *in vacuo* to give an oil **29** (0.535 g, 0.00135 mol, 91%). Since all attempts to crystallize the oil failed, the purity of the product was checked by thin layer chromatography (5% ethyl acetate–benzene on silica gel plates). For the oil **29**: ir (CH_2Cl_2) 6.01 (C=O) and 8.20–8.50 μ (mesylate); $[\alpha]^{20}D$ +22.7° (*c* 0.227, CH_2Cl_2); no halogen (negative $AgNO_3$ test).

Reaction of α-Bromopropiophenone with Optically Active Methylphenyl-*n*-propylphosphine.—To α-bromopropiophenone (0.963 g, 0.0045 mol) in dry glyme (5 ml) was added (−)-**30** [0.75 g, 0.0045 mol, $[\alpha]^{20}D$ −16.1° (as above)] with stirring. After 24 hr, the white solid was filtered off (five crops) to give α-methylphenacyl methylphenyl-*n*-propylphosphonium bromide (**27**): 0.75 g, 0.00197 mol, 44%; mp 160–163°; $[\alpha]^{20}D$ +36.4° (*c* 0.532, CH_2Cl_2): ir (CH_2Cl_2) 5.95 (C=O), 8.21, and 10.9 μ; nmr ($CDCl_3$) τ 1.0–2.5 (m, 10, phenyl H), 3.1–3.5 (m, 1, methine H), 7.39 (d, 3, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), 8.20 (q, CCH_3, J_{HH} = 8, $J_{^{31}PH}$ = 3 Hz), 8.52 (q, CCH_3, J_{HH} = 7.5, $J_{^{31}PH}$ = 3 Hz), 6.5–7.5 and 8.1–8.6 (m, 4, methylene H), and 8.9 (m, 3, methyl H).

Reaction of (+)-27 with Silver Mesylate.—To (+)-**27** (0.60 g, 0.0015 mol) in acetonitrile (50 ml) was added silver mesylate (0.50 g, 0.0024 mol) as above, to give an oil: pure by tlc (5% ethyl acetate–benzene on silica gel plates); ir (CH_2Cl_2) 6.0 (C=O) and 8.35 μ (mesylate); $[\alpha]^{20}D$ +20.2° (*c* 0.480, CH_2Cl_2); no halogen (negative $AgNO_3$ test).

Reaction of α-Chlorobenzyl Phenyl Ketone (2) with Optically Active Methylphenyl-*n*-propylphosphine.—To **2** (1.04 g, 0.0045 mol) in dry glyme (5 ml) was added (−)-**30** (0.75 g, 0.0045 mol). After the mixture was stirred for 24 hr, a white solid was filtered off in several crops to give α-phenylphenacyl methylphenyl-*n*-propylphosphonium chloride (**32**): 0.94 g, 0.00324 mol, 72%; ir (CH_2Cl_2) 3.2–3.7, 6.0, 6.3, 6.95, 7.4–7.9, 8.0–8.5, 9.0, 9.9, 10.0, and 14.5 μ; nmr ($CDCl_3$) τ 1.25–3.0 (m, 15, phenyl and methine H), 7.35 (d, 1.5, CH_3, $J_{^{31}PCH_3}$ = 14 Hz), 7.60 (d, 1.5, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), 6.6–8.8 (m, 4), and 9.05 (m, 3, CCH_3); $[\alpha]^{20}D$ +68.5° (*c* 0.475, CH_2Cl_2).

Reaction of (+)-32 with Silver Mesylate.—A mixture of (+)-**32** (0.50 g, 0.00126 mol) and silver mesylate (0.75 g, 0.0037 mol) was stirred overnight in acetonitrile (100 ml) and treated as above, to give α-phenylphenacyl methylphenyl-*n*-propylphosphonium mesylate (**33**, 0.506 g, 0.00111 mol, 88%), $[\alpha]^{20}D$ +17.8° (*c* 0.797, CH_2Cl_2). The oil was pure by tlc (5% ethyl acetate–benzene on silica gel plates): ir (CH_2Cl_2) 5.9 (C=O) and 8.2–8.4 μ (mesylate); no halogen (negative $AgNO_3$ test).

Reaction of α-Mesyloxybenzyl Phenyl Ketone (31) with (−)-30.—A mixture of **31** (1.76 g, 0.00604 mol) and (−)-**30** [1.0 g, 0.00604 mol, $[\alpha]^{20}D$ −15.6° (CH_3OH)] was heated at reflux for 2 hr in dry glyme (10 ml). After the mixture was cooled at 5–10° for 3 days, a white solid was filtered off to give α-phenylphenacyl methylphenyl-*n*-propylphosphonium mesylate (2.26 g, 0.00495 mol, 82%): mp 137–141°; ir (CH_2Cl_2) 5.9 (C=O) and 8.2–8.4 μ (mesylate); nmr ($CDCl_3$) τ 1.7–2.8 (m, 16, phenyl, methine H), 7.2 (s, 3, mesylate H), 7.45 (d, 1.5, methyl, $J_{^{31}PCH_3}$ = 14 Hz), 7.65 (d, 1.5, methyl, $J_{^{31}PCH_3}$ = 14 Hz), 8.7–9.1 (t, 3, methyl H), and 6.7–8.6 (m, 4, methylene H); $[\alpha]^{20}D$ +29° (*c* 0.525, CH_2Cl_2).

Anal. Calcd for $C_{25}H_{28}OSP$: C, 65.77; H, 6.40. Found: C, 65.64; H, 6.46.

Reaction of α-Mesyloxypropiophenone with (−)-30.—α-Mesyloxypropiophenone (1.37 g, 0.00604 mol) and (−)-**30** (1.0 g, 0.00604 mol, $[\alpha]^{20}D$ −15.6°) were heated at reflux for 2 hr in dry glyme (10 ml). Isolation as above gave α-methylphenacyl methylphenyl-*n*-propylphosphonium mesylate (**29**): 0.285 g, 0.000725 mol, 12%; mp 140–141.5°; $[\alpha]^{20}D$ +3.7° (*c* 0.817, CH_2Cl_2); ir (CH_2Cl_2) 6.0 (C=O) and 8.20–8.50 μ (OSO_2CH_3); nmr ($CDCl_3$) τ 1.7–2.7 (m, 10, phenyl H), 3.90–4.3 (m, 1, methine H), 7.3 (s, 3, mesylate), 7.55 (d, 3, methyl, $J_{^{31}PCH_3}$ = 14 Hz), 8.4 (q, 3, methyl, J_{HH} = 8 Hz, $J_{^{31}PCH_3}$ = 18 Hz), 6.8–8.7 (m, 4, methylene H), and 8.8–9.3 (m, 3, methyl H).

Anal. Calcd for $C_{20}H_{27}O_4SP$: C, 60.89; H, 6.89. Found: C, 60.79; H, 6.97.

Base Hydrolysis of Optically Active Ketophosphonium Salts.—α-Bromopropiophenone reacted with (+)-**30**, $[\alpha]^{20}D$ +12.0°, to give the ketophosphonium bromide (**27**, 62%, $[\alpha]^{20}D$ −24.7°).

Anal. Calcd for $C_{19}H_{24}OBrP$: C, 60.17; H, 6.38. Found: C, 59.98; H, 6.48.

The bromide (−)-**27** (0.186 g, 0.00049 mol) was hydrolyzed with 10% aqueous NaOH (4 ml, 0.01 mol) at reflux for 24 hr to give, after Et_2O extraction, drying, and evaporation, a yellow oil (0.134 g) which contained propiophenone (0.0543 g, 82%) and (−)-**35** (0.079 g, 89%) crude, $[\alpha]^{20}D$ −8.74° by nmr analysis. The oil was chromatographed on basic alumina (Merck, Brockman grade I, 25 g) to give propiophenone (0.021 g, 32%, ether elution) and (−)-**35** [0.079 g, 89%, CH_3OH elution, $[\alpha]^{20}D$ −8.02° (*c* 0.53, CH_3OH) after sublimation at bath temperature of 60° and collector temperature of −78°]; nmr spectra were identical with genuine samples. The ketophosphonium chloride (+)-**32**, from α-chlorobenzyl phenyl ketone and (−)-**30** ($[\alpha]^{20}D$ −16.1°, 0.0728 g, 0.000202 mol) was similarly hydrolyzed to give benzyl phenyl ketone **44** (0.0289 g, 73%, mp 53–55°), and (+)-**35** [0.0362 g, 99%, $[\alpha]^{20}D$ +11.19° (*c* 0.19, CH_3OH)]. Both products were identical with genuine samples (by nmr, mmp 53–55° for ketone with genuine **44** of mp 53–56°). Base hydrolysis of *dl*-**32** had previously given **44** (57%) and *dl*-**35** (79%).

Conversion of (−)-27 to Keto Ylide 34 and Reaction of 34 with Benzaldehyde.—Treatment of (−)-**27** (0.188 g, 0.000497 mol) with 10% aqueous NaOH (5 ml, 0.013 mol) in tetrahydrofuran (10 ml) for 10 min, extraction with Et_2O (four 5-ml portions), drying, and evaporation of the organic layer gave crude keto ylide **34** (0.160 g) as a syrupy white solid. Benzaldehyde (0.0673 g, 0.000634 mol) in tetrahydrofuran (30 ml) was added, and the mixture was heated at reflux for 24 hr and then cooled. Evaporation *in vacuo* gave a yellow oil (0.252 g) which was chromatographed on Merck basic alumina (25 g) to give the chalcone **36** [0.0914 g, 0.000411 mol, 83%, petroleum ether and ether elution; uv max (95% EtOH) 228 nm (log ε 3.96), 251, (4.02), and 289 (4.09) (lit.[39] uv max for *trans*-**36** (95% EtOH), 225 nm (log ε 4.02), 260 (4.05), and 290 (4.24); nmr spectrum ($CDCl_3$) identical with genuine sample] and (+)-**35** [0.0879 g, 0.00055 mol, 97% (CH_3OH elution); $[\alpha]^{20}D$ +4.54° (*c* 1.36, CH_3OH)].

The Wittig Reaction of α-Methylphenacyltriphenylphosphorane 45 with Benzaldehyde.—Reaction of ylide **45** (2.214 g, 0.00561 mol) with benzaldehyde (0.613 g, 0.00577 mol) in tetrahydrofuran (70 ml) for 24 hr at reflux gave a crude mixture (2.62 g) which was chromatographed on Fisher alumina (A-540, 25 g) to give the chalcones **36a** and **36b** [petroleum ether elution, 0.988 g, 0.0044 mol, 79%; uv max (95% EtOH) 223.5, 260, and 290 nm; mass spectrum (70 eV) *m/e* (rel intensity) 222 (62, $M\cdot^+$), 221 (42), 179 (7), 178 (4), 145 (10), 144 (7), 131 (8), 117 (20), 115 (36), 105 (100), 91 (17), and 77 (98); nmr ($CDCl_3$) τ 2.1–3.0 (m, 11, phenyl and vinyl H), 7.75 (d, 2.8, CH_3 of **36a**, J = 1.7 Hz), and 7.87 (d, 0.2, CH_3 of **36b**, J = 1.4 Hz)] and triphenylphosphine oxide [Et_2O, CH_3OH elution, 1.44 g, 92%; mp 152–155°, mmp 153–156° with genuine sample (mp 155–156°); ir and nmr spectra identical with genuine sample].

The assignment of the trans configuration **36a** to the major isomer is based on previous uv evidence for the trans nature of **36** as formed by aldol condensation,[39] and on the fact that Wittig reactions of stabilized ylides give predominantly the trans olefinic product.[40]

Reaction of α-Bromodimedone with (−)-30.—α-Bromodimedone (5.7 g, 0.026 mol) and (−)-**30** [4.32 g, 0.026 mol, $[\alpha]^{20}D$ −11.6° (methanol)] were mixed in $CDCl_3$ (15 ml) at −78°. After the mixture was stirred for 5 days, the solvent was removed *in vacuo*. Distillation of the residual oil gave 5,5-dimethyl-3-bromocyclohexenone [4.2 g, 0.0205 mol, 79%, bp 60° (0.025 mm)] and methylphenyl-*n*-propylphosphine oxide [3.22 g, 0.0176 mol, 68%, bp 110° (0.025 mm), $[\alpha]^{20}D$ 0.0° (*c* 0.471, C_2H_5OH)].

(39) W. B. Black and R. E. Lutz, *J. Amer. Chem. Soc.*, **77**, 5134 (1955).

(40) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 253.

Reaction of α,α-Dibromobenzyl Phenyl Ketone with (−)-30.—To a solution containing **6** (6.39 g, 0.01806 mol) in dry glyme (50 ml) was quickly added (−)-**30** (3.0 g, 0.01806 mol, $[\alpha]^{20}D$ −12.1° (*c* 4.92, CH_3OH). The mixture was stirred overnight at 0° to give **38** (9.1 g, 0.0178 mol, 98%): $[\alpha]^{20}D$ −5.42° (*c* 1.45, CH_2Cl_2); ir (CH_2Cl_2) 3.2–3.5, 8.2, 8.9, 9.2–9.6, and 10.3–10.6 μ; nmr ($CDCl_3$) τ 1.65–3.1 (m, 15, phenyl H), 7.25 (d, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), 7.7 (d, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), and 6.8–9.2 (m, 7, propyl H). A repetition using **30**, $[\alpha]^{20}D$ −11.6°, gave **38** (63%), $[\alpha]^{20}D$ −5.10° (*c* 1.45, CH_2Cl_2).

Reaction of Optically Active 38 with Sodium Hydroxide.—To **38** [7.0 g, 0.0134 mol, $[\alpha]^{20}D$ −5.42° (*c* 1.45, CH_2Cl_2)] in methylene chloride (100 ml) was added sodium hydroxide (100 ml, 10%). The solution was stirred for 2 hr, each layer separated, and the water portion extracted with methylene chloride (500 ml). After drying, the solvent was removed *in vacuo* and the residual oil distilled to give methylphenyl-*n*-propylphosphine oxide (**35**): 1.2 g, 0.007 mol, 49%; $[\alpha]^{20}D$ −5.2° (*c* 12.5, CH_3OH); nmr ($CDCl_3$) τ 1.7–2.6 (m, 5, phenyl H), 8.4 (d, 3, methyl H, $J_{^{31}PH}$ = 13.5 Hz), and 8.0–9.2 (m, 7, propyl H). A repetition using **38**, $[\alpha]^{20}D$ −5.1°, gave **35** (43%), $[\alpha]^{20}D$ −4.6° (*c* 12.5, CH_3OH).

The Hydrolysis of Enol Phosphonium Salts with Sodium Hydroxide Enriched with O^{18}.—A solution of *dl*-**38** (0.280 g, 0.000538 mol, from **6** and *dl*-**30**) in CH_2Cl_2 (5 ml) was added to 10% aqueous $NaO^{18}H$ [from sodium (0.27 g, 0.019 g-atom) and 10% O^{18}-enriched "low deuterium" water (5.00 g)] and then stirred for 2 hr. Removal of the organic layer, extraction of the water layer with CH_2Cl_2 (two 1-ml portions), combination of the organic layers, drying, and evaporation *in vacuo* at 25° gave a yellow oil (0.23 g) which was chromatographed on Merck basic alumina (25 g) to give **1** (90%) and O^{18}-enriched **35** (0.0838 g, 0.00046 mol, 86%, CH_3OH elution): mass spectrum (7 eV) *m/e* (rel intensity) 182 (100, $M\cdot^+$), 183 (18.21), 184 (14.03), 154 ($M\cdot^+ - C_2H_4$, 83.6), 155 (7.9), 156 (10.9), 139 (81.4, $M\cdot^+ - C_3H_7$), 140 (6.8), and 141 (11.3). Oxygen-16 **35** has a mass spectrum (7 eV) *m/e* (rel intensity) 182 (100), 183 (11.36), 184 (1.24), 154 (34.7), 155 (3.6), 156 (0.1), 139 (14.4), 140 (0.2), and 141 (0.1). On the basis of these data, scale expanded data at these peaks, and corrections for natural abundance of isotopes, the O^{18}-enriched **35** was estimated to have 10.9–11.5% O^{18} enrichment; *i.e.*, all of the original 10% enrichment was retained.[41,42]

In a similar manner, **14** was hydrolyzed with $NaO^{18}H$ to give **39** (81%) and triphenylphosphine oxide (94%): mass spectrum (10 eV) *m/e* (rel intensity) 278 (100, M), 279 (27.61), and 280 (15.26). Oxygen-16 triphenylphosphine oxide had 278 (100, M), 279 (19.24), and 280 (2.79). The enriched triphenylphosphine oxide from **14** was calculated to have 10.7% O^{18} enrichment; *i.e.*, again all of the excess O^{18} was retained.[42]

Reactions of 38 Attempted with Tributylphosphine or Trisdimethylaminophosphine.—To an nmr tube containing α,α-dibromobenzyl phenyl ketone (0.240 g, 0.000679 mol) in $CDCl_3$ (1 ml) was added **30** (0.113 g, 0.000678 mol). The nmr spectrum indicated complete formation of the enol phosphonium salt **38**. To the mixture was added tributylphosphine (0.137 g, 0.000679 mol). After 1 hr, nmr indicated a complete absence of reaction. A similar attempted reaction with trisdimethylaminophosphine also failed.

Reaction of Optically Active Methylphenyl-*n*-propylphosphine with α-Bromopropiophenone and Water.—Methylphenyl-*n*-propylphosphine [3.7 g, 0.0222 mol, $[\alpha]^{24}D$ −13.7° (CH_3OH)] was added to a mixture of α-bromopropiophenone (4.75 g, 0.0222 mol), water (9 ml), and dioxane (21 ml). After 10 min the solvent was removed *in vacuo* to give an oil which was dissolved in methylene chloride and dried, and the solvent removed *in vacuo*. Distillation of the residual oil gave methylphenyl-*n*-propylphosphine oxide (3.6 g, 0.0197 mol, 89%): $[\alpha]^{20}D$ 0.0° (CH_3OH); bp 110° (0.025 mm); nmr ($CDCl_3$) as above.

Treatment of the Enol Phosphonium Bromide 14 with Aniline.—A mixture of **14** (5.33 g, 0.0083 mol) and aniline (0.93 g, 0.01 mol) was stirred under nitrogen in acetonitrile (100 ml) at 25° for 40 min, methanol (10 ml) was added, the solvent evaporated, and the residue extracted with benzene to give as an insoluble fraction, anilinotriphenylphosphonium bromide **40** [CH_2Cl_2 soluble, 0.16 g, 0.00037 mol, 4%; mp 200–201°; ir and nmr identical with genuine sample] and aniline hydrobromide (CH_2Cl_2 insoluble, 0.23 g, 0.0013 mol, 16%).

The benzene soluble fraction contained methyltriphenylphosphonium bromide (0.12 g, 0.0003 mol, 4%), triphenylphosphine oxide, aniline, diphenylacetophenone (by tlc), and traces of other products.

Reaction of α-Bromo-α,α-diphenylacetophenone with TPP and Aniline.—Under similar reaction conditions as above, the bromo ketone **8** (3.5 g, 0.01 mol), TPP (2.62 g, 0.010 mol), and aniline (0.93 g, 0.01 mol) were stirred for 20 min, methanol was added, and the procedure outlined above was used to give **40** (3.84 g, 0.0088 mol, 88%), aniline hydrobromide (0.114 g, 0.0007 mol, 7%), diphenylacetophenone, triphenylphosphine oxide (by tlc), trace amounts of other products, and no aniline.

Anilinotriphenylphosphonium Bromide 40.—Bromine (3.20 g, 0.020 mol), in benzene (20 ml) was added dropwise to a mixture of triphenylphosphine (5.24 g, 0.020 mol) and aniline (6.00 g, 0.065 mol) in benzene (50 ml). The resultant mixture was heated at reflux for 2 hr and kept at 25° overnight, and the resulting solid was extracted with chloroform which was evaporated to give an oil which was triturated with benzene to give crude anilinotriphenylphosphonium bromide (4.42 g, 0.010 mol, 50%, mp 112–120°). Two recrystallizations from methanol–ethyl acetate gave white crystals: mp 201–202°; ir ($CHCl_3$) 3.40 (s), 3.65 (m), 6.25 (m), 6.70 (m), 6.90 (m), 8.20 (m), 8.92 (s), 10.30 (s), and 14.90 μ (s); nmr ($CDCl_3$) τ 3.77 (m, 5), 3.20 (m, 15), −0.75 (d, 1, *J* = 9 Hz).

Anal. Calcd for $C_{24}H_{21}BrNP$: C, 66.36; H, 4.84; Br, 18.45; N, 3.22; P, 7.15. Found: C, 66.18; H, 4.96; Br, 18.60; N, 3.41; P, 7.18.

Registry No.—**10**, 26709-95-5; **12**, 26709-96-6; **13a**, 26710-02-1; **14**, 26709-97-7; **15**, 26709-98-8; **27** (+), 26709-55-7; **27** (−), 26709-61-5; **28**, 26709-56-8; **29**, 26731-54-4; **30** (±), 20108-75-2; **30** (−), 13153-89-4; **32**, 26731-55-5; **35** (*dl*), 2328-23-6; **35** (+), 17170-48-8; **35** (−), 1515-99-7; **36a**, 14182-01-5; **36b**, 26709-60-4; **38**, 26697-55-2; **40**, 6395-93-3; **43**, 26710-00-9; **44**, 451-40-1; methyldiphenylphosphine, 1486-28-8; 5,5-dimethyl-3-bromocyclohexanone, 13271-49-3.

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(41) One of the methods used by us is found in K. E. DeBruin and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 7393 (1969). Our error is greater (*ca.* 10%).

(42) The phosphine oxides and ketones resulting from these hydrolyses were identical with genuine samples (ir, nmr, and melting point).