TOPICS IN
STEREOCHEMISTRY

EDITORS

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Professor of Chemistry
University of Notre Dame
Notre Dame, Indiana

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VOLUME 5

WILEY-INTERSCIENCE

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To the 1969 Nobel Laureates
in Chemistry
DEREK H. R. BARTON
and
ODD HASSEL

INTRODUCTION TO THE SERIES

During the last decade several texts in the areas of stereochemistry and conformational analysis have been published, including *Stereochemistry of Carbon Compounds* (Eliel, McGraw-Hill, 1962) and *Conformational Analysis* (Eliel, Allinger, Angyal, and Morrison, Interscience, 1965). While the writing of these books was stimulated by the high level of research activity in the area of stereochemistry, it has, in turn, spurred further activity. As a result, many of the details found in these texts are already inadequate or out of date, although the student of stereochemistry and conformational analysis may still learn the basic concepts of the subject from them.

For both human and economic reasons, standard textbooks can be revised only at infrequent intervals. Yet the spate of periodical publications in the field of stereochemistry is such that it is an almost hopeless task for anyone to update himself by reading all the original literature. The present series is designed to bridge the resulting gap.

If that were its only purpose, this series would have been called "Advances (or "Recent Advances") in Stereochemistry." It must be remembered, however, that the above-mentioned texts were themselves not treatises and did not aim at an exhaustive treatment of the field. Thus the present series has a second purpose, namely to deal in greater detail with some of the topics summarized in the standard texts. It is for this reason that we have selected the title *Topics in Stereochemistry*.

The series is intended for the advanced student, the teacher, and the active researcher. A background of the basic knowledge in the field of stereochemistry is assumed. Each chapter is written by an expert in the field and, hopefully, covers its subject in depth. We have tried to choose topics of fundamental import, aimed primarily at an audience of organic chemists but involved frequently with fundamental principles of physical chemistry and molecular physics, and dealing also with certain stereochemical aspects of inorganic chemistry and biochemistry.

It is our intention to bring out future volumes at approximately annual intervals. The Editors will welcome suggestions as to suitable topics.

We are fortunate in having been able to secure the help of an international board of Editorial Advisors who have been of great assistance by suggesting topics and authors for several articles and by helping us avoid duplication of topics appearing in other, related monograph series. We are grateful to the

Editorial Advisors for this assistance, but the Editors and Authors alone must assume the responsibility for any shortcomings of *Topics in Stereochemistry*.

N. L. Allinger
E. L. Eliel

January 1967

PREFACE

Volume 5 continues our annual publication schedule of *Topics* in *Stereochemistry*. There appears to be no shortage of topics to be discussed or of competent authors willing to discuss them. The increased number of chapters in Volume 5—six, as compared to four in each of the previous volumes—is in part a reflection of this fact.

This volume, for the first time, presents a trend which will, undoubtedly become more important in future volumes: some of the subjects represent, in some measure, elaborations of certain aspects of chapters published earlier. Thus, a very brief account of the stereochemistry of the Wittig reaction was included in the chapter on stereochemical aspects of phosphorus chemistry by Gallagher and Jenkins in Volume 3. In the intervening two years, the subject developed to the point where it merits treatment of its own at greater length. Dr. Manfred Schlosser, in the first chapter, presents a carefully organized and quite detailed summary of the stereochemistry of the Wittig reaction. His chapter should be of interest not only to those interested in the mechanism of what has become one of the major reactions in organic synthesis, but also to those chemists who wish to exploit the synthesis in a practical way to prepare pure *cis* or *trans* olefins.

The second chapter, by G. Krow, deals with a rather classical subject: the stereochemistry of compounds which owe their chirality to the presence of chiral axes or chiral planes rather than chiral centers. Although the *concepts* of chiral axes and chiral planes were only recently defined, the chiral axis was first recognized by van't Hoff himself in allenes, and spiranes and alkylidenecycloalkanes were resolved shortly after the turn of the century. The chiral plane seems to have made its first appearance in Lüttringhaus' ansa compounds in 1940. By now, a very large body of experimental material has accumulated and a review seems timely, especially since a number of absolute configurations of compounds of this type have been elucidated recently. It might be pointed out that Schlögl's chapter in Volume 1 deals with a particular class of compounds (the metallocenes) having a chiral plane.

Increasingly, stereochemical concepts are of interest in molecules of biochemical import. The third chapter, by M. Goodman, A. S. Verdini, and N. S. Choi, deals with the stereochemistry and conformation of polypeptides. In this chapter are brought together the results obtained by numerous physical techniques: ultraviolet, infrared, and nuclear magnetic resonance spectro-

scopy, optical rotatory dispersion, and circular dichroism—as well as by theoretical approaches, based on both statistical mechanics and semi-empirical calculation of conformation. This chapter should be of interest to those working in the fields of statistical mechanics, as well as to polymer chemists and to physical biochemists.

Volume 3 contained a chapter by Binsch on measurement of energy barriers by nmr. The topic of energy barriers and stable ground-state conformations is elaborated in two chapters in the present volume: the fourth chapter by G. J. Karabatsos and D. J. Fenoglio and the fifth chapter by E. Wyn-Jones and R. A. Pethrick. The former chapter deals mainly with the stable conformations of relatively small molecules about single bonds adjacent to double bonds. The latter chapter, in contrast, is oriented methodologically toward the determination of energy barriers by ultrasonic relaxation and infrared spectral methods, thus complementing the earlier chapter dealing with nmr. It might be mentioned here that a compilation of barriers and stable conformations of saturated molecules (by J. P. Lowe) has appeared in Volume 6 of the Streitwieser-Taft series *Progress in Physical Organic Chemistry*.

The sixth and last chapter by J. McKenna deals with the interpretation of quaternization rates in conformationally mobile amines. This is an area in which there has been much activity recently and also a certain amount of confusion in the interpretation of the data. Dr. McKenna has organized the experimental material carefully, considered it critically, and stated what conclusions may and may not be drawn. Hopefully, this chapter contains a lesson useful in other mechanistic studies.

We are dedicating this volume to Derek H. R. Barton and Odd Hassel who, on December 10, 1969, received the Nobel Prize for their pioneering work in the field of conformational analysis. The impact of conformational analysis on the progress of stereochemical thinking has been enormous; without it there would probably be no need for this Series. Suffice it to say that two chapters (the fourth and fifth) in the present volume and four in the four previous volumes are more or less directly concerned with conformational ideas and two additional ones in this volume (the third and sixth chapters) bear a strong relation, so our indebtedness to the 1969 Nobel Laureates is very evident.

Norman L. Allinger
Ernest L. Eliel

January 1970

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VOLUME 5

A WILEY-INTERSCIENCE SERIES

The Stereochemistry of the Wittig Reaction

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ABSTRACT

Stereochemical control in Wittig olefin syntheses may be accomplished in three different ways:

1. In salt-free solution the normal tendency of ylids is to combine with aldehydes to give betainlike intermediates which are very largely in the *erythro* configuration. If betaine formation can be made irreversible, high amounts of *cis* olefins will thus be obtained.

2. Several types of olefinic compounds, such as stilbenes and α,β-unsaturated ketones and esters, are significantly more stable as *trans* isomers than as *cis* isomers. Wittig reactions will afford such products *trans*-stereoselectively if equilibration of the intermediate betaines through reversible decomposition to the reactants is rapid.

3. In the presence of lithium salts, the adducts from triphenylphosphonium alkylids and aldehydes are thermodynamically much more stable in the *threo* configuration. Betaine equilibration is conveniently achieved by α-metallation followed by reprotonation of the resultant β-oxido phosphorus ylids. After completion of the reaction sequence, almost pure *trans* olefins can be isolated, provided that subsequent epimerizations are excluded.

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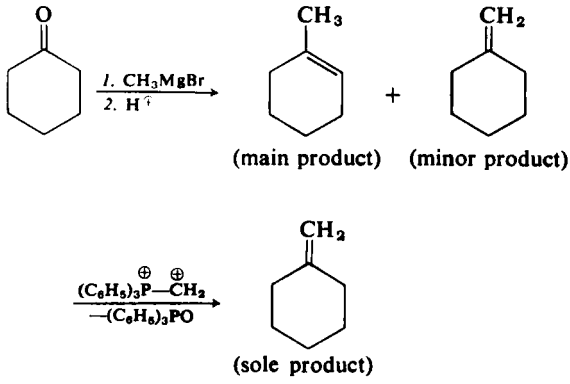
Stereochemical implications as well as preparative applications of these procedures will be pointed out. Reaction rates, reversibility of betaine formation, and stereoselectivity are affected by the "stationary" ligands bound to the phosphorus atom, by the nature of the solvent, and by special additives, such as carboxylic acids or inorganic salts. These effects on the reaction will be discussed under mechanistic and practical aspects.

I. INTRODUCTION

Only a few years after its discovery, the Wittig carbonyl olefination reaction by means of phosphorus ylids has become a favorite tool in preparative organic chemistry (1–3). One of the main virtues of this synthetic method is its complete structural specificity. While, for instance, the addition of a Grignard reagent to a carbonyl compound followed by dehydration normally leads to a mixture of positionally isomeric olefins, the new carbon–carbon double bond created in the Wittig reaction appears exclusively at the site of the former carbonyl function (4) (eq. (1)).



(1)

Despite this structural specificity, the Wittig synthesis may yet afford more than one olefin if the reaction product exhibits *cis–trans* isomerism. Indeed, the classical paper of Wittig and Schöllkopf (4) already mentions that the reaction between α-monosubstituted phosphorus methylids and aldehydes produces *cis* and *trans* olefins in about equal amounts. This finding was in agreement with expectation and so at that time the carbonyl olefination reaction seemed to offer no stereochemical problems. But soon Bohlmann et al. (5) recognized that phosphorus alkylids do not necessarily react nonstereoselectively, but may in fact preferentially yield the thermodynamically less stable *cis* olefins in some instances. Many other investigators were able to confirm this puzzling observation (6–10) and special credit must be given to Shemyakin and co-workers (11–13), who were the first to study the *cis* selectivity systematically and to point out its preparative value.

The first case of the opposite stereoselectivity was revealed by House and Rasmusson (14). They demonstrated that the condensation of triphenylphosphonium carbomethoxy-ethylid with acetaldehyde led to a mixture of isomeric α,β-unsaturated methyl esters, $CH_3CH{=}C(CH_3)COOCH_3$, in which the thermodynamically more stable tiglic acid derivative (*E* configuration) prevailed in a ratio of 96:4 over the less stable angelic acid ester, which bears the carbomethoxy residue on the same side of the double bond as the vicinal methyl group, i.e., has the *Z* configuration. Later, *trans*-selectivity was found to be a general feature of the Wittig reaction wherever so-called "stable" ylides are involved, that is to say, ylids bearing a powerful electron-attracting substituent, such as carbonyl or carboxyl functions, in the α-position to the phosphorus atom. Moreover, the *trans*-selectivity is preserved when the phenyl groups linked to the phosphorus are exchanged for other "stationary" ligands, even if one switches from ylids derived from phosphonium salts to the α-carbanions of phosphine oxides or phosphonic acid esters (15).

Any attempt to rationalize the complex stereochemistry of olefin formation will have to be concerned with the mechanism of the Wittig reaction. Unfortunately many mechanistic details of this reaction have not yet been satisfactorily elucidated. Thus, it is even uncertain whether the reacting system (ylid plus carbonyl compound) passes, on its way to phosphine oxide and olefin, through an open-chain zwitterion, i.e., a betaine, through a cyclic oxaphosphetane (16), or through both of them consecutively. The reaction sequence depicted in Figure 1 has no other merit than that of being believed to be the most probable one.

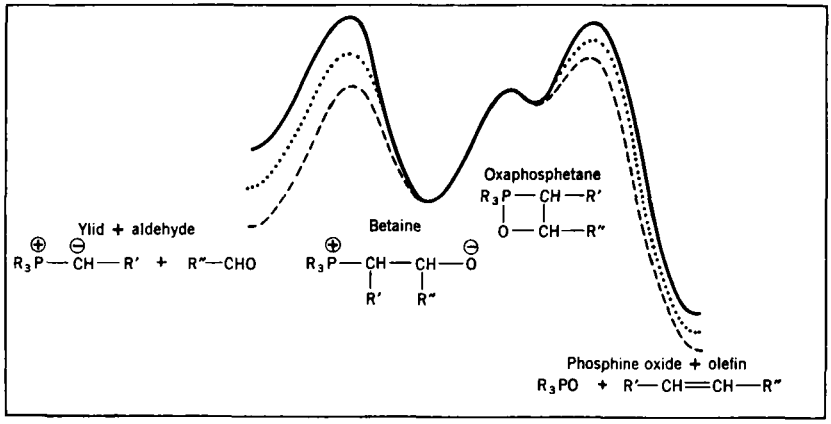
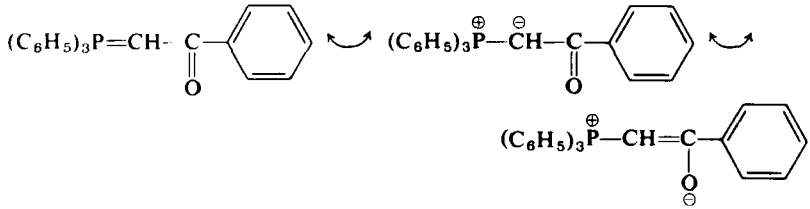


Fig. 1. (Assumed) energy profile of the Wittig carbonyl olefination reaction, effected by (——) "reactive", (· · · ·) "moderated" or (----) "stable" phosphonium ylids. (In the following figures the hypothetical oxaphosphetane intermediate will be omitted, since it has no further bearing on the discussion.)

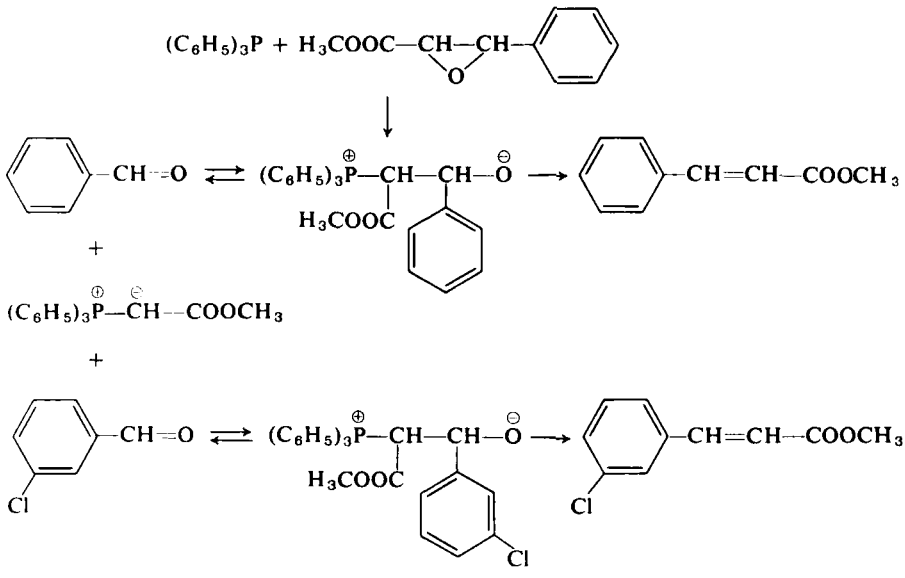
Closely related to the olefin-forming process are cyclopropane (17–19) and epoxide (20) forming ylid reactions. Nevertheless, this chapter will be restricted to stereochemical effects governing the *cis–trans* ratios of products obtained in olefin syntheses. Accordingly, the configurational changes (21–24) at the phosphorus atom in the course of the Wittig reaction will also be disregarded.

II. STEREOSELECTIVITY IN REACTIONS OF STABLE YLIDS

So-called stable ylids are characterized by extensive delocalization of the negative charge through participation of resonance structures, e.g.,



Because of the relatively low basicity of resonance-stabilized ylids, their addition to carbonyl compounds is an endergonic process. Thus, as is frequently observed in aldol-type reactions, no reaction intermediates can be

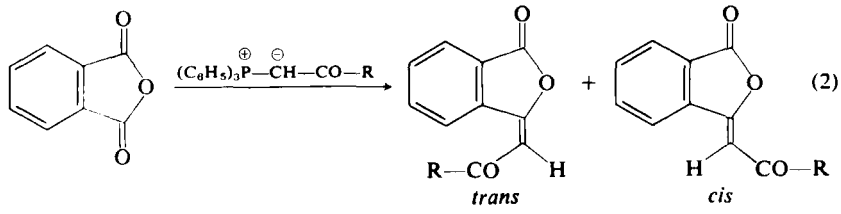


Scheme 1

captured. Yet, the hypothetical zwitterionic intermediates turned out to be accessible by an independent route, thus offering an elegant means for demonstrating the reversibility of betaine formation involving stable ylids. The addition of triphenylphosphine to phenylglycidic ester afforded a betaine which was cleaved rapidly and reversibly to yield benzaldehyde and triphenylphosphonium carbomethoxymethylid which could be trapped by added *m*-chlorobenzaldehyde (25) (Scheme 1).

The *trans* stereoselectivity of olefin syntheses effected with stable ylids may now be explained as follows (14). The reactants combine to give a betaine with either an *erythro* or *threo* configuration, the two species being in equilibrium. This intermediate eliminates triphenylphosphine oxide completely irreversibly, and in a *cis* manner (21), so that the *erythro* and *threo*-betaine must give *cis* and *trans* olefin, respectively. Because of conjugation, the *trans* isomer is approximately 4 kcal/mol more stable and it is reasonable to assume that the corresponding transition state is also lowered in energy to some extent. As a consequence, the *threo* epimer is preferentially consumed, but is continuously replenished by the mobile equilibrium through which both betaine diastereoisomers can be rapidly interconverted. Under these circumstances an overall preference of the *threo* → *trans* route by one or two powers of ten is what one might expect (see Fig. 2).

Resonance-stabilized phosphorus ylids need not, however, always yield the thermodynamically more stable olefins. If the carbonyl compound is highly reactive and the nucleophilicity of the ylid is not too low, the reversible decomposition of the reaction intermediates may be outrun by the triphenylphosphine oxide elimination, in which case product formation will be kinetically controlled. In this way it may be understood why phthalic anhydride affords the *trans* olefin by action of triphenylphosphonium carbamidomethylid and carbalkoxymethylids, but the *cis* olefin by action of triphenylphosphonium acetylmethylid and a 1:4 mixture of both by action of triphenylphosphonium phenacetylid (26) (eq. (2)).



(2)

$R = NH_2$	> 10 : 1
$R = OCH_3$	> 10 : 1
$R = C_6H_5$	1 : 4
$R = CH_3$	< 1 : 10

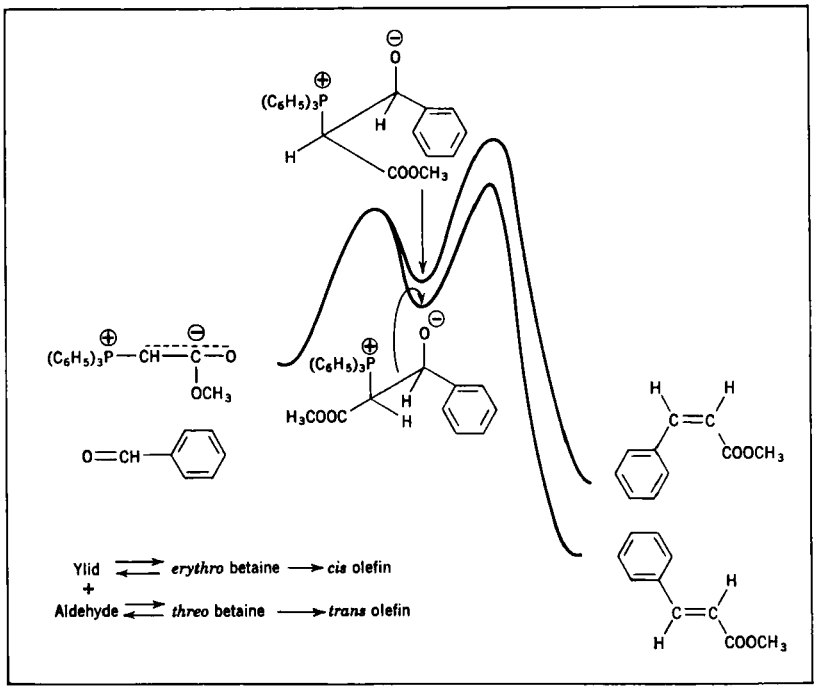


Fig. 2. Energy profile for the reaction between a stable phosphorus yield and an aldehyde. The eclipsed betaine conformations are not expected to be the most highly populated; they are depicted in this manner only for the sake of clarity.

Similarly, the less stable *trans* isomer (or *E* isomer) results from the reaction of triphenylphosphonium carbethoxymethylid with *N*-methylphthalimide (27).

Still somewhat obscure is the puzzling catalytic effect of weakly acidic additives on the reaction rates of stable ylids. In a typical case, the formation of cinnamic ester from triphenylphosphonium carbomethoxymethylid and benzaldehyde in benzene solution is accelerated by a factor of about 20 upon addition of one equivalent of benzoic acid. Replacement of dimethylformamide by methanol as the solvent leads to a rate enhancement by a factor of over 100 (28). Obviously, all the species involved in this carbonyl olefination reaction, including the phosphine oxide (29), can act as hydrogen-bond acceptors and, therefore, their energy levels will be lowered by proton-donor substances. But the weakly polar oxaphosphetane and the transition state will, of course, be less stabilized by hydrogen bonding than the ylid and betaine zwitterions, so that one might have predicted an overall rate decrease. Since the contrary is true, an additional effect must be operative. One possible mode of operation might be hydrogen bonding to the ester residue at the

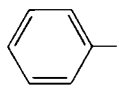
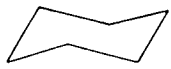
oxaphosphetane stage. In this manner electron demand increases at the position neighboring the phosphorus atom, an effect which is known to assist the elimination of triphenylphosphine oxide from the intermediate. Some further ideas in this respect may be derived from the report (30) that the cleavage of oxiranes yielding carbonyl compounds and olefins is accelerated by acid catalysis.

If the height of the second energy barrier is really reduced relative to the first barrier upon hydrogen bonding (see Fig. 3), this change should lead, at least in some cases, to a shift in isomer distribution. Indeed, in the reaction between phosphorus carbalkoxymethylids and aliphatic (31) or aromatic (32) aldehydes, the amount of the *cis* isomer in the product mixture increases significantly if an aprotic solvent is replaced by a protic one or if soluble lithium salts are added. For instance, triphenylphosphonium carbethoxymethylid and benzaldehyde afford *cis*- and *trans*-cinnamic esters in the ratio 2:98 if benzene serves as the solvent (28), but in the ratio 15:85 if the reaction is carried out in ethanol (32).

On the other hand, the *trans*-stereoselectivity is improved if the "stationary" phenyl ligands are replaced by alkyl groups (Table I). Alkyl substitution destabilizes the phosphorus ylid (33), but causes a considerable stabilization of phosphine oxides (29) and by extrapolation, since the phosphorus atom is then even more electron demanding, particularly of betaines. The olefin-generating transition state, however, will be lowered in energy content to a much lesser extent. This can easily be seen if one makes the reasonable assumption that the transition state resembles the oxaphosphetane in which the phosphorus atom bears only a small charge, if any. As a consequence,

TABLE I

cis–trans Ratios for Ethyl Cinnamate Resulting from the Interaction Between Different Phosphorus Carbethoxymethylids and Benzaldehyde in Ethanol at 25°C

R in $R_3\overset{\oplus}{P}-\overset{\ominus}{C}H-COOC_2H_5$	 $-CH=CH-COOC_2H_5$ *cis–trans* ratio
	15:85
n-C_4H_9	5:95
n-$C_{10}H_{21}$	4:96
	1:99

the energy barrier, which must be overcome in going from the betaine to the olefin, rises and the *erythro–threo* equilibration through reversible betaine decomposition becomes more successful (Fig. 3).

Wittig reactions effected with "moderated" ylids, such as triphenylphosphonium benzylid, are usually devoid of marked stereoselectivity (31–31b), although the principles governing the stereochemical course of these reactions are the same as in the case of olefination reactions through "stable" ylids. The reason for the difference is that aryl, alkenyl, and alkinyl residues at the position α to the phosphorus atom cause less effective resonance stabilization than, say, acyl, carbalkoxy, or cyano groups. As a consequence, betaine formation is only weakly endergonic and the rates of forward and backward decomposition of the intermediate are frequently of the same order of magnitude. Accordingly, electron-donating substituents which enhance the nucleophilicity of the ylid reduce the *trans*-stereoselectivity, while electron-withdrawing ligands increase it (34,35) (Scheme 2). Conversely, the *cis*-stereoselectivity of triphenylphosphonium propinylid (36) indicates that it is less effectively resonance stabilized than triphenylphosphonium allylid (4,37), which usually yields *cis–trans* isomer mixtures with a slight preponderance of the *trans* olefin.

A delicate balance of rate-retarding and rate-accelerating effects seems to be responsible for the changes in stereochemistry observed when moderated ylids are allowed to react in the presence of protic solvents or soluble lithium salts. A careful study of stilbene formation from methyldiphenylphosphonium benzylid and benzaldehyde has revealed (38) that reversible

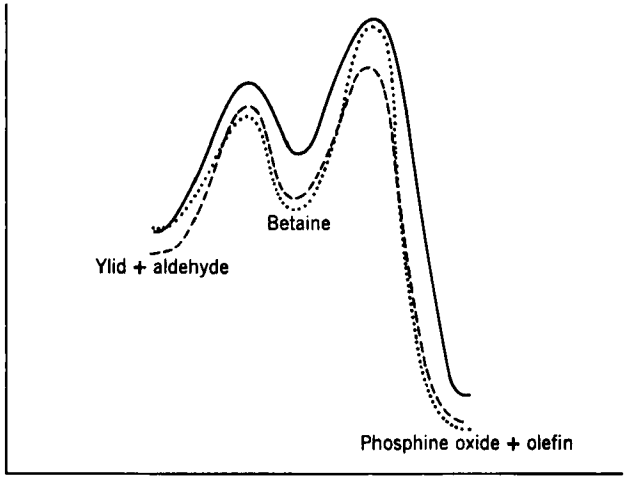
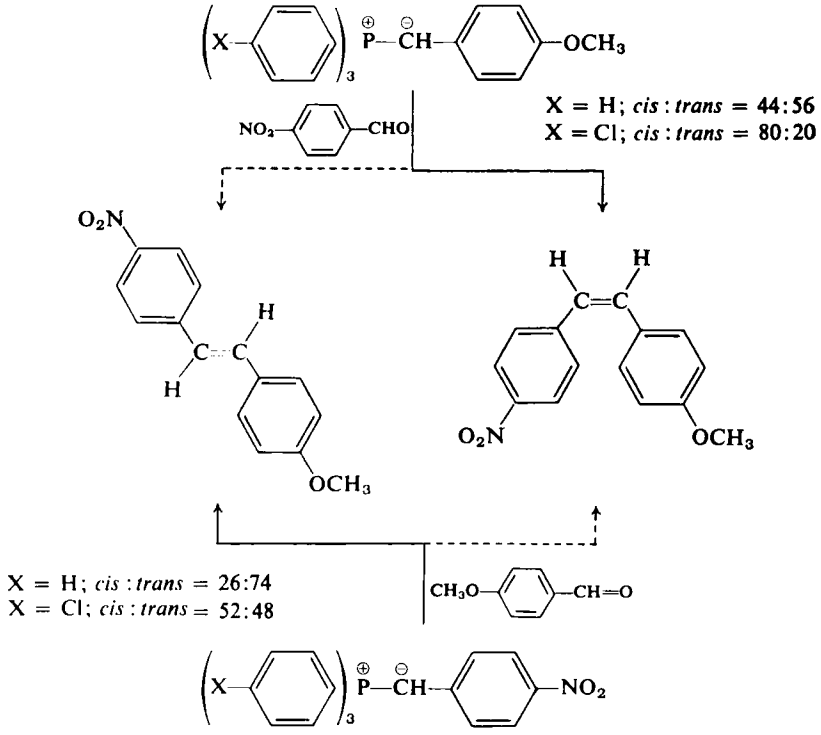


Fig. 3. Energy profile of cinnamic ester formation by action of tri*phenyl*phosphonium carbethoxymethylid (——) in benzene and (----) in ethanol and (· · · ·) by tricy*clohexyl*-phosphonium carbethoxymethylid in ethanol.



Scheme 2

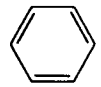
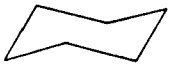
betaine decomposition is slow compared to triphenylphosphine oxide elimination in aprotic solution. The "reversibility factor" which may be defined as the ratio *k*(*erythro* betaine → reactants)/*k*(*erythro* betaine → *cis* olefin) ranges from 0.1 in dimethyl sulfoxide to 3.3 in methanol. Correspondingly, the *cis–trans* ratio in the two solvents decreases from 47:53 to 22:78. In tetrahydrofuran in the presence of lithium bromide, an even higher proportion of *cis*-stilbene (*cis*:*trans* = 53:47) is obtained (39) (Table II).

A comparison of the distribution of stilbene isomers obtained from ethanol solutions clearly demonstrates that the more alkyl groups replace phenyl groups at the phosphorus atom, and the bigger these groups are, the more *trans* olefin results (Table II). As already stated above, the electron-rich alkyl residues lower the energy level of the betaine intermediate relative to the olefin-generating transition state and thus enhance the rate of betaine equilibration through reversible decomposition.

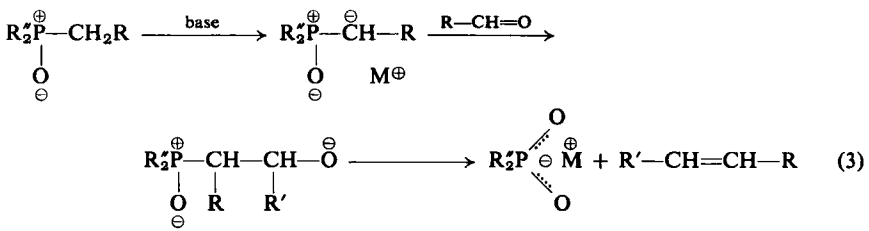
In principle, the same change is observed on passing from the "$P^{\oplus}$ ylids," derived from triphenylphosphonium salts, to the "PO ylids," as we may call the carbanions of phosphine oxides and phosphonic esters. In

TABLE II

Relative Yields of *cis*- and *trans*-Stilbene from the Reaction of Different Phosphorus Benzylids $RR'R''\overset{+}{P}-\overset{-}{C}HC_6H_5$ with Benzaldehyde at Room Temperature

Solvent	R, R′, R″ =  (ref. 39, 53)	R = CH_3, R′, R″ =  (ref. 38)	R, R′, R″ = *n*-C_4H_9 (ref. 39)	R, R′, R″ =  (ref. 40)
Tetrahydrofuran/LiBr	67:33	53:47		—
Dimethyl sulfoxide	—	47:53	—	—
t-Butanol	—	32:68	—	—
Ethanol	58:42	28:72	9:91	5:95
Methanol	47:53	22:78	—	—
Benzene/toluene	44:56	—	—	—

contrast to the rapid reaction of PO ylids with aldehydes in the addition step of the olefination sequence, the second, product-forming step can, in general, be brought about only if the intermediate is activated at the position α to phosphorus. The corresponding betaines containing a phosphinyl group and the final phosphorus acid salts are so stable that the transition state in between becomes very unfavorable. Therefore, the "PO modification" is limited mainly to the preparation of diarylethylenes and α,β-unsaturated carbonyl compounds (3,41) (eq. (3)).

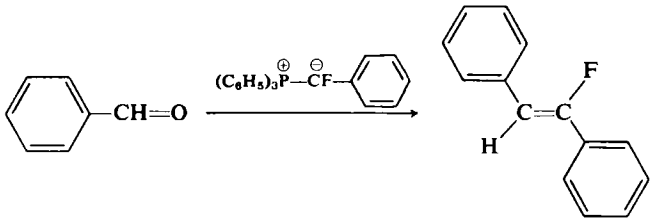


(3)

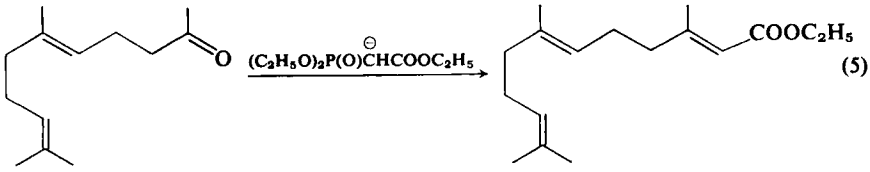
$R'' = C_6H_5, C_2H_5O \ldots$

$R = C_6H_5, COCH_3, COOC_2H_5, CN \ldots$

As exemplified above, a low barrier between the intermediate adduct and the reactants and a high barrier separating the intermediate from the products constitute excellent conditions for diastereoisomeric equilibration. As a consequence, the *trans* isomers, which are considerably more stable than the *cis* isomers in the series of stilbenes or α,β-unsaturated carbonyl compounds,



(4)

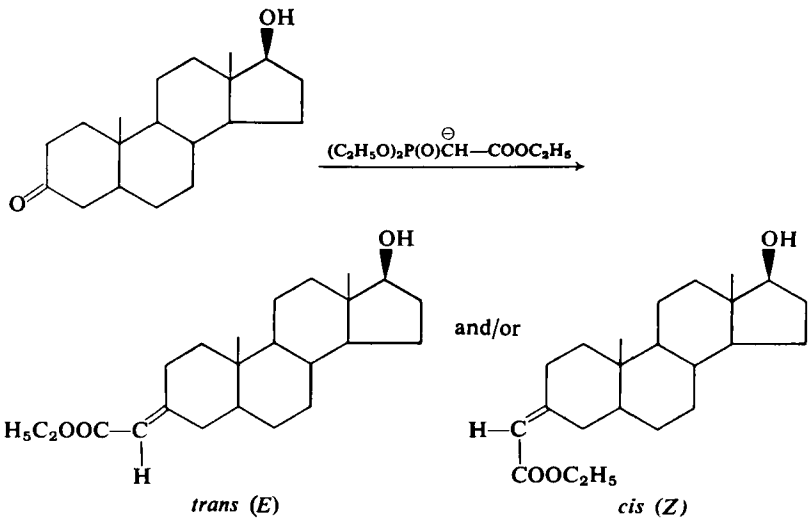


(5)

80–90% isomerically pure

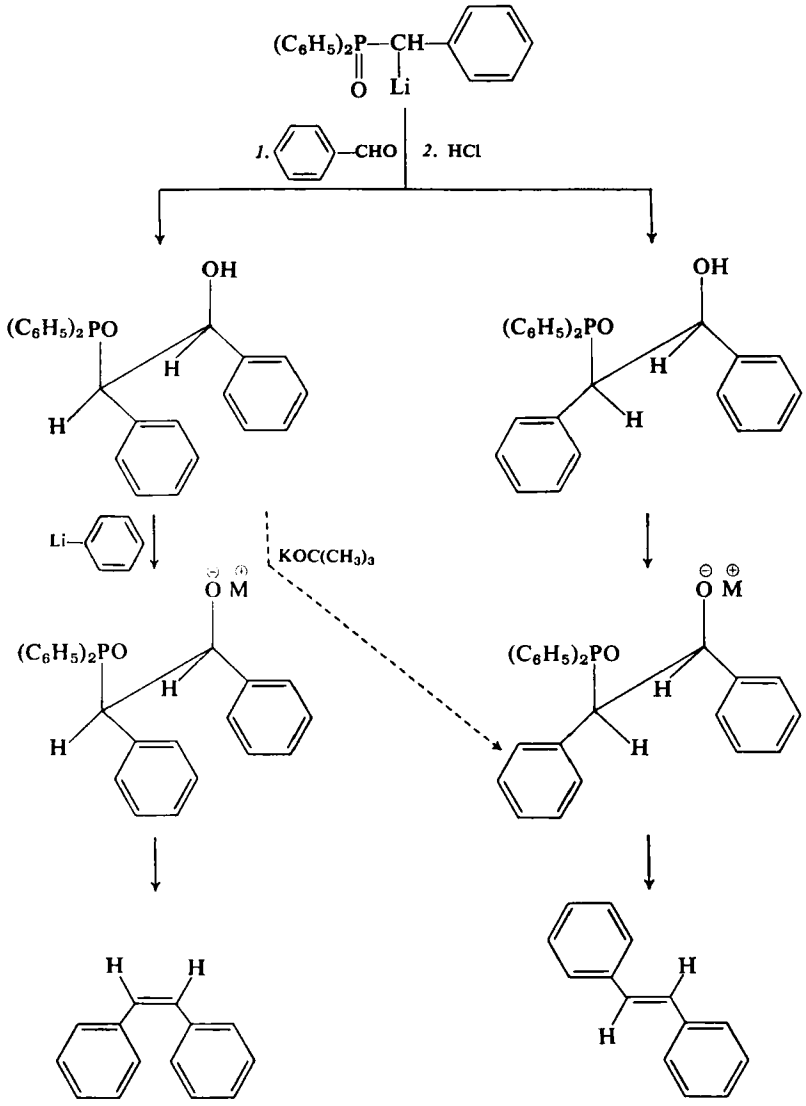
should be formed preferentially or almost exclusively. Indeed, in all PO-activated carbonyl olefinations so far investigated, the proportion of the *trans* isomer exceeded 90% (in most cases 96%) (42).

If a trisubstituted ethylene is produced in the reaction between an α,α-disubstituted phosphonate and an aldehyde, the aldehydic residue will normally show up at the olefinic double bond in the position *trans* to that ylid ligand which has the higher "mesomeric potential" in order to minimize steric hindrance to resonance (43–45) (eq. (4)). By the same token, the principal isomer resulting from the interaction of an unsymmetrical ketone and an unbranched PO ylid contains the larger ketone residue and the former ylid side chain on opposite sides of the double bonds (46,47) (eq. (5)).



trans (E) *cis (Z)*

In view of the consistency observed throughout, it remains somewhat mysterious why the stereochemical outcome should depend on the nature of the base utilized for phosphonate generation to the extent that is reported for the condensation between diethyl carbethoxymethylphosphonate and dihydrotestosterol. In the presence of sodium hydride the steroid derivative



M = Li, K

Scheme 3

with the ester group placed in the position *trans* to ring B was found to be the sole product, while the *cis* product seemed to predominate when the reaction was carried out by means of potassium *t*-butoxide (48) (eq. (6)).

It became possible to study, in detail, the ability of the zwitterionic intermediate to equilibrate after accomplishment of successful isolation and separation of the *erythro–threo* mixture of (β-hydroxy-α,β-diphenylethyl)-diphenylphosphine oxide, which had been prepared by action of α-lithium benzyldiphenylphosphine oxide on benzaldehyde followed by hydrolysis. Upon treatment with exactly one equivalent of phenyllithium and heating, the *erythro* component afforded pure *cis*-stilbene. However, when potassium *t*-butoxide served as the base, only *trans*-stilbene could be isolated (49) (Scheme 3).

III. STEREOSELECTIVITY IN REACTIONS OF REACTIVE YLIDS

The addition step of most Wittig reactions brought about by means of stable or moderated ylids has been found to occur endergonically. But even if a highly nucleophilic PO ylid, such as α-lithium benzyldiphenylphosphine oxide, is involved, a rapid equilibrium between the zwitterionic reaction intermediate and the reactants will be established on account of the very great height of the second activation barrier. This situation changes profoundly as soon as we pass on to the so-called "reactive" phosphorus ylids, that is to say, ylids with a saturated aliphatic side chain. The interaction of such a reactive ylid with a carbonyl group is usually an exergonic process. In addition, the olefin-generating transition state lies low enough to ensure that the betaine intermediates are converted predominantly to the products before returning to the reactants. (Fig. 4).

A more detailed study has revealed that the reaction between triphenylphosphonium alkylids and primary *aliphatic* aldehydes is irreversible within the limits of experimental precision. Some reversible decomposition is observed if *α,β-unsaturated* or *aromatic* aldehydes serve as carbonyl components. Thus, addition of excess *m*-chlorobenzaldehyde to the preformed adduct from triphenylphosphonium methylid and benzaldehyde at −50°C followed by warming to about −25°C resulted in the formation of 6% *m*-chlorostyrene in addition to 70% styrene itself. Since the introduction of alkyl groups at the position α to the phosphorus atom slows down the elimination of triphenylphosphine oxide by one order of magnitude, reversible return is enhanced in these compounds. Thus, upon decomposition in the presence of *m*-chlorobenzaldehyde, the adduct from triphenylphosphonium ethylid and benzaldehyde yields 39% β-methylstyrene and 42% *m*-chlorophenylpropene (50).

If both forward steps of the Wittig reaction sequence are completely

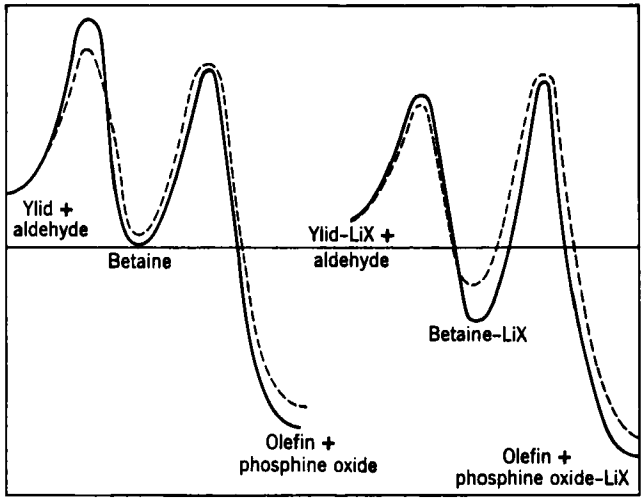


Fig. 4. Energy profiles of the reaction between triphenylphosphonium ethylid and propanal (left) in the absence and (right) in the presence of soluble lithium salts. *erythro* → *cis* course (----); *threo* → *trans* course (——).

irreversible, the olefin *cis–trans* ratio strictly reflects the *erythro–threo* composition of the intermediate betaine. Even in the case of partial reversibility the isomeric composition of the final reaction products still allows a fair estimate on the primary distribution of betaine diastereoisomers. Interestingly, all the stereochemical results observed lead to the conclusion that, particularly in salt-free solution, the formation of the *erythro* betaine is greatly favored over the formation of the *threo* betaine. *cis–trans* Ratios measured for the reaction of triphenylphosphonium ethylid with aliphatic and aromatic aldehydes are always greater than 85:15 provided the aldehyde is not highly electrophilic. Homologous unbranched triphenylphosphonium alkylids actually yield an average *cis–trans* distribution of 95:5 (Table III) (50–52) (eq. (7)).

$$(C_6H_5)_3\overset{\oplus}{P}-\overset{\ominus}{C}H-CH_2R + R'-CH=O \longrightarrow \underset{\text{Main product}}{\overset{H}{\underset{R'}{\diagdown\!\!\diagup}}C=C\overset{H}{\underset{CH_2R}{\diagdown\!\!\diagup}}} + \underset{\text{Minor product}}{\overset{R'}{\underset{H}{\diagdown\!\!\diagup}}C=C\overset{H}{\underset{CH_2R}{\diagdown\!\!\diagup}}} \qquad (7)$$

R, R′: residues to be chosen arbitrarily

It has been recommended (53) that *cis*-stereoselective carbonyl olefinations be carried out in salt-free benzene, toluene, or tetrahydrofuran solutions at 0°C. In another convenient procedure a mixture of the phosphonium salt