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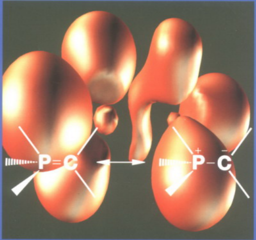
Phosphorus Ylides

Chemistry and Application in Organic Synthesis



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Oleg I. Kolodiazhnyi

Phosphorus Ylides

Chemistry and Application in Organic Synthesis

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To my daughters, Anastasia and Olga

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List of Abbreviations

1-Ad	adamant-1-yl
Alk	alkyl
All	allyl
Ar	aryl or aromatic
Ar*	2,4,6-tri-tert-butylphenyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	tertiary butyl
s-Bu	secondary butyl
t-Bu	isobutyl
Bz	benzyl
cat.	catalyst
cm	centimeter
Cp	cyclopentadienyl
Cp*	pentametylcyclopentadienyl
*	centre of chirality
d	doublet
DBN	1,5-diazobicyclo[4,3,0]non-5-ene
DBU	1,8-diazobicyclo[4,4,0]undec-7-ene
dd	double doublet
dec.	decomposition
diglyme	bis(2-methoxyethyl)ether (ethyleneglycoldimethylether)
DME	1,2- dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dq	double quartet
dt	double triplet
Et	ethyl
eV	electron volt
Fc	ferrocen
FVP	flash-vacuum pyrolysis
FVT	flash-vacuum thermolysis
g	gram
h	hour
Hlg	halogen
HMPT	hexamethylphosphotriamide
i-Pr	isopropyl
IR	infrared
kg	kilogram
L	liter
liq.	liquid
LT	leukotrienee
m-	*meta-*
m	multiplet
M	molar
Me	methyl
Me_3Si	trimethylsilyl
Mes	2,4,6-trimethylphenyl (mesityl)
mL	milliliter
mm	millimeter
mp	melting point
Mnt	menthyl
MS	mass spectrum
n-	normal
N	normal (concentration)
nm	nanometer
NMR	nuclear magnetic resonance
o-	*ortho-*
p-	*para-*
Pnt	pentyl
PG	prostaglandin
Ph	phenyl
Pr	propyl
i-Pr	isopropyl
R_F	perfluoroalkyl
q	quartet
s	second or singlet (NMR)
s- or *sec-*	secondary
sept	septet
t- or *tert.-*	tertiary
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
Ts	$4\text{-}MeC_6H_4SO_2$ (tosyl)
UV	ultraviolet

Phosphorus Ylides: Chemistry and Application in Organic Synthesis
by Oleg I. Kolodiazhnyi
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1 Introduction

The phosphorus ylides is an outstanding achievement in the chemistry of the twentieth century[1]. Phosphorus ylides have found use in a wide variety of reactions of interest to synthetic chemists, especially in the synthesis of naturally occurring products, compounds with biological and pharmacological activity. The development of the modern chemistry of natural and physiologically active compounds would have been impossible without the phosphorus ylides. These compounds have attained great significance as widely used reagents for linking synthetic building blocks with the formation of carbon–carbon double bonds, and this has aroused much interest in the study of the synthesis, structures and properties of P-ylides and their derivatives. Every year approximately 120–150 new articles dedicated to phosphorus ylides are published. At present the list of publications on phosphorus ylides includes more than 4000 articles and patents, of which no fewer than 800 have been published since 1990. The chemistry of the phosphorus ylides is nowadays studied in such detail that it has become one of the fundamental divisions of classical organic chemistry.

Unfortunately the chemistry and, especially, the application of phosphorus ylides in organic synthesis has not been sufficiently systematized. Some aspects of the chemistry of phosphorus ylides have been treated from time to time in reviews[2–11] or described as chapters in books.[12-13] One example, the monograph of A.W. Johnson[12], dedicated to several classes of compound (*Phosphorus Ylides, Phosphorus Imines, Phosphonate Carbanions, Transition Metal Complexes*), describes the application of phosphorus ylides too briefly. Some types of phosphorus ylide which have explored the most intensively in recent years, for example C-heterosubstituted ylides, C-metallated ylides, P-heterosubstituted ylides, phosphacumulene ylides, and carbodiphosphoranes, are discussed insufficiently in this book.

At the same time the current state of knowledge of phosphorus ylide chemistry requires review and publication of the most important achievements in the chemistry and the application of these important reagents. Therefore we bring to the attention of readers our monograph, the purpose of which is to present the state of the chemistry and the application of phosphorus ylides in organic synthesis. This book is intended for the practising organic chemist and its major objective is to familiarize the reader with the more important transformations that can be conveniently brought about in the laboratory by use of these reagents.

The applications of phosphorus ylides that have been collected in this book were chosen principally for their general usefulness in organic synthesis. Coverage, of necessity, is selective rather than comprehensive. Practical details are given, and where possible illustrative procedures have been selected that do not require the use of special techniques or complex and expensive equipment. Sufficient details are given about reaction conditions to enable preliminary evaluation of procedures for particular applications. The experimental details that are provided in many examples are helpful in this respect, and extensive references to the original literature are given so that further information can be obtained when necessary. In most cases the procedures described use phosphorus ylides that are either available commercially or are easily prepared. The cross-references given in the text and the extensive indexes are intended to unify the material and to make easily accessible all of the relevant information that is available on each topic. The book covers the literature published until 1998, for the most part results obtained in the last 10–15 years.

This book will be of special use and interest to chemists who need a reference to particular application of ylide chemistry and those who perform research in ylide chemistry for its own sake and who wish to be brought up to date on some aspect of this chemistry.

1.1 Historiography

Phosphorus ylides were synthesized for the first time more than 100 years ago. At the end of nineteenth century Mikhaelis and co-workers reported the synthesis of some phosphorus ylides, although they proposed an incorrect structure for them[14] and only 50–60 years later was it shown (Aksness[15a], Ramirez and Dershowitz[15b]) that first ylides were prepared by Michaelis. The work of Michaelis and Gimborn was an isolated occurrence and did not attract chemists' special attention to ylides.

In 1919 Staudinger and Meyer synthesized and correctly characterized triphenylphosphonium diphenylmethylide.[16,17] In work published in 1921, on the reaction of this ylide with diphenylketene and phenylisocyanate, they found, for the first time, the reaction which was to be named the Wittig reaction. Unfortunately, Staudinger did not recognize the large synthetic possibilities of the reaction of phosphorus ylides with carbonyl compounds and his work was not developed.

In the next few years studies devoted to the ylides of phosphorus were conducted only sporadically. Only in 1949 did G. Wittig[18] observe that treatment of tetramethylphosphonium salts with phenyllithium led to the formation of trimethylphosphonium methylide[18] and in 1953 Wittig and Geissler[19] discovered that triphenylphosphonium methylide reacts with the benzophenone to form 1,1-diphenylethylene and triphenylphosphine oxide.

$$[Ph_3PMe]^+Br^- \xrightarrow{PhLi} Ph_3P{=}CH_2 \xrightarrow{Ph_2C=O} Ph_2C{=}CH_2 \qquad (1)$$

This discovery led to the development of a new method for the preparation of alkenes which has since found widespread application in synthetic organic chemistry and is now universally known as the Wittig reaction. It was very soon shown that this reaction is generally applicable, is of high selectivity, and proceeds without rearrangement and isomerization.

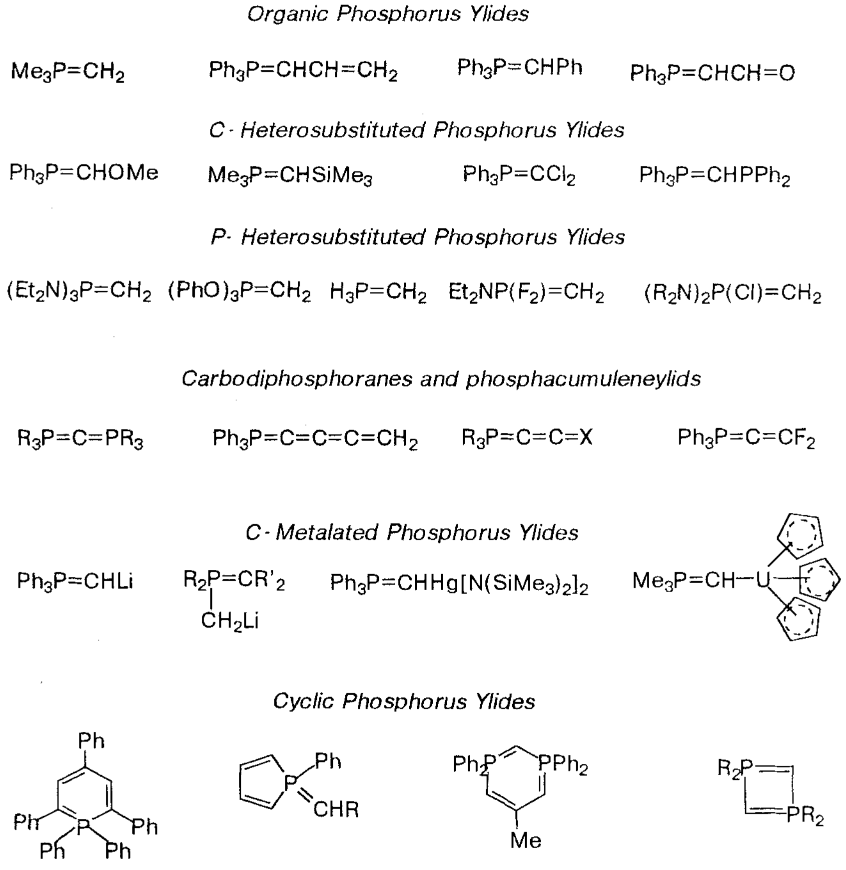
At the beginning of the 50s work aimed at the industrial synthesis of vitamin A was begun at BASF research[20] and at the same time Wittig discovered the olefination of carbonyl compounds by phosphorus ylides. Owing to the close relations existing in Germany between university scientists and industrial chemists Wittig's discovery was very soon known in the BASF laboratories. Reppe and Pommer working in the laboratories of BASF immediately recognized the significance of the Wittig reaction for the synthesis of vitamin A-type compounds. They invited G. Wittig to their laboratory and in a few days only the synthesis of retinoic acid was successfully carried out by means of the new reaction. Retinoic acid prepared by this process is used in pharmaceutical preparations as an active ingredient against acne. The industrial synthesis of Vitamin A was then begun in the BASF Aktiengesellschaft by use of this process. This was the beginning of the wide application of the Wittig reaction in organic synthesis; this was subsequently recognized by the award of the Nobel Prize to Wittig.[1,21–23]

After 1953 the chemistry of phosphorus ylides progressed intensively. Outstanding achievements in the development of phosphorus ylide chemistry were contributed by Bestmann,[24,25] Corey,[26] Schlosser,[11] Trippett,[27] Seyferth,[28] and many other chemists. It was found that phosphorus ylides not only react with carbonyl compounds, but can also be used in many nucleophilic reactions and are in no way inferior to Grignard compounds with regard to the variety of possible reactions. New chapters and directions of phosphorus ylide chemistry were created, for instance the chemistry of the ylidic complexes of transition metals (Schmidbaur,[29] Kasca,[30] Cramer,[31] Karsch[32]), C-elementsubstituted P-ylides (Schmidbaur,[3] Corey,[26] Burton[33]), P-heterosubstituted phosphorus ylides (Kolodiazhnyi,[6-8] Appel,[34] Fluck[35]), cumulene ylides (Bestmann[24]), carbodiphosphoranes (Ramirez et al.[36]). Corey[37] and Bestmann[5] developed methods for the synthesis of natural and biologically active compounds—antibiotics, prostaglandins, leukotrienes, based on phosphorus ylides. Vedejs[38], Maryanoff,[9] and McEven[39] et al. studied the mechanism of the Wittig reaction in detail. Streitwisser,[40] Dixon,[41] Bock,[42] and Gilheany[43] et al. carried out theoretical investigations of the nature of P=C bonding in ylides.

In recent years the chemistry of metallated phosphorus ylides has been developed by Cristau.[44] Schmidpeter,[45] Bertrand,[46] and Grutzmacher[47] have used phosphorus ylides as the starting building blocks for the preparation of organophosphorus compounds of unusual coordination.

1.2 Types of Phosphorus Ylides and Structure of Book

At the present time a large amount of material has been accumulated on the chemistry of phosphorus ylides. Various classes of these compounds have been synthesized. Therefore the question about the classification of different types of phosphorus ylide is well-timed. In the chemical literature phosphorus ylides are usually considered as *stabilized, semi-stabilized,* and *non-stabilized,* depending on the delocalization of the negative charge on the ylidic carbon atom by substituents. However it is difficult to construct the monograph in accordance with such classification, because chapters become too large. At the same time it is quite natural to classify the material on the basis of the nature of the atoms or groups connected to the phosphorus and carbon atoms of the P=C bond. In this book, therefore, chapters are devoted to *C,P-carbon-substituted phosphorus ylides, C-element-substituted phosphorus ylides, P-heterosubstituted phosphorus ylides, carbodiphosphoranes, phosphacumulene ylides* with specific chemical properties, and a chapter considering the physicochemical properties of the phosphorus ylides. Chapters, in their turn, are divided into sections depending on the structures of the carbon-containing groups or elements of the periodic table connected directly to the carbon and phosphorus atoms of the P=C group.



Scheme1

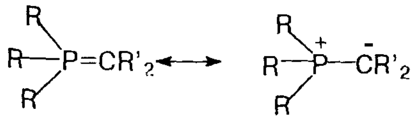
The book deals with ylide chemistry and its application in organic synthesis for the preparation of naturally occurring products, compounds with biological and pharmacological activity, prostaglandin, leukotrienes, steroids, antibiotics, sugars, terpenoids, insect pheromones, pesticides, etc. The chapters in this book show how one can obtain fragments of such products, with emphasis in most instances on the more practical methods, illustrated by experimental preparations of the most important phosphorus ylides and their transformations developed or revised in the author's laboratory. The book proposes synthetic recommendations and examples of ylide applications in organic synthesis.

The book is organized into six chapters. Chapter 1 is the Introduction. C,P-carbon-substituted phosphorus ylides, the most important class of phosphorus ylide, their preparation, chemical properties and application in organic synthesis, are presented in Chapter 2. Chapter 3 deals with phosphacumulene ylides and carbodiphosphoranes, their chemical properties and application in the synthesis of natural products. Chapter 4 describes the application of C-heterosubstituted and C-metal-substituted phosphorus ylides in organic synthesis. Chapter 5 discusses the chemistry of P-heterosubstituted phosphorus ylides and their application as building blocks in a variety of preparations. The Wittig Reaction and its application in organic synthesis are described in Chapter 6, which contains sections, describing examples of the application of phosphorus ylides for the preparation of cyclic compounds (small-, middle- and macrocycles), pharmaceutical substances (leukotrienes, prostaglandins antibiotics, vitamins), steroids, pheromones, juvenoids, and pyrethroids, and in industrial applications.

The book emphasizes practical aspects of organic synthesis using phosphorus ylides and it is appropriate that some chapter sections are concerned with the preparation of a particular class of compound (*e.g.* the preparation of prostaglandins or leukotrienes), whereas others deal with a particular type of reaction (*e.g.* photolysis, flash-vacuum pyrolysis, and [2+2]- or [2+3]-cycloadditions). In this way each section has its own distinct character. The cross-references given in the text and the extensive indexes are intended to unify the material and to make easily accessible all the relevant information available on each topic.

1.3 Nomenclature

Before proceeding to the description of the phosphorus ylides, it is necessary to discuss the nomenclature of these compounds. The ground state of phosphorus ylides can be described by two canonical structures—*ylene* **A** and *ylide* **B**.



A **B**

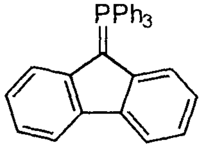
(2)

The first of these canonical structures (ylenic formula **A**) postulates the existence of double bonding between the phosphorus and carbon atoms. The second (ylidic formula **B**) reflects the highly polar zwitterionic nature of the ylidic P=C group and is a consequence of the existence of phosphonium center near a carbanion center, the negative charge of which can be delocalized by substituents connected to the ylidic carbon atom. Modern theoretical calculations and experimental physical methods show that the bipolar ylidic structure makes the most contribution to the ground state of phosphorus ylides. The contribution of the ylenic structure arises from the probable $(d\text{–}p)_\pi$ interaction of the pair of free electrons on the carbon atom with the vacant *d*-orbitals of the phosphorus atom. However, detailed studies of the electronic structure of ylides lead to the conclusion that this contribution is minimal[48]. In accordance with the existence of two resonance structures **A** and **B** two nomenclatures exist for phosphorus ylides. The first assumes the presence of true multiple-bonding P–C and defines phosphorus ylides as R_5 phosphorane derivatives. In compliance with this nomenclature, ylides can be named *alkylidenephosphoranes*. This nomenclature is convenient and is therefore widely used. Its application is reasonable in that the phosphorus ylides are usually described by the ylene rather than the ylide structure. However this nomenclature does not reflect the true structure of ylides because the contribution of the ylene structure is minimal. It is, therefore, more correct to name ylides as *phosphonium alkylides* or *phosphonium methylides,* regarding these compounds as carbanions, the negative charge of which is neutralized by phosphonium cations directly attached to them. According to this definition the name 'ylide' denotes a species with a carbon group, indicated by the suffix '*yl*' (from the radical 'alkyl') bearing a negative charge (corresponding to a heteropolar bond), indicated by the suffix '*ide*' (by analogy with methanide), located on a carbon directly linked to a heteroatom bearing a positive charge (onium). The full name of ylides can be constructed in this manner—first indicate the substituents on the phosphorus atom, and then according to the rules of the IUPAC nomenclature name the carbanion part of a molecule by adding the term (*ylide=yl+id*). For instance:

$Ph_3P{=}CR'_2$

1

triphenyl-methylenephosphorane
triphenylphosphonium methylide
triphenylphosphonium methanide



2

triphenyl-fluorenylenephosphorane
triphenylphosphonium fluorenylide
triphenylphosphonium fluorenide

It is also justifiable to name the phosphorus ylides in accordance with the requirements of IUPAC nomenclature to use the suffix '*yd*', attached to the name of an appropriate hydrocarbon, from which the carbanion (methanide, ethanide, fluorenide and so on) was obtained. In this case the phosphonium cation is visualized as a substituent attached to the carbanion. Therefore the name of a phosphorus ylide consists of two moieties—the phosphonium cation and the carbanion—triphenylphosphonium methanide, triphenylphosphonium fluorenide, triethylphosphonium ethanide and so on. In the last few years, some authors have used this nomenclature[49].

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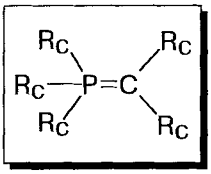
2

C,P-Carbon-Substituted Phosphorus Ylides

2.1 Introduction

Ylides bearing organic (i.e. carbon-based) substituents on the phosphorus and carbon atoms of the P=C group (organic ylides of phosphorus) are the most numerous and important representatives of this class of compound.



In the earliest days of ylide chemistry almost all P-ylides were C,P-carbon-substituted. Only in recent years has the chemistry of phosphorus ylides of other types, in particular C- and P-heterosubstituted phosphorus ylides, been extensively developed.[1] Depending on the substituents on the carbon atom of the P=C bond, C,P-carbon-substituted ylides can be classified into several types with individual physical and chemical properties.

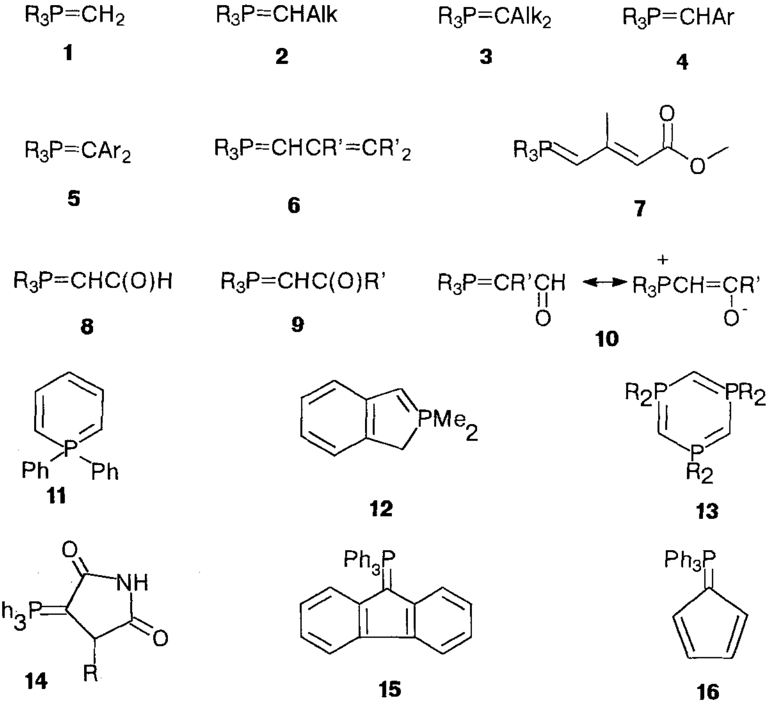
2.1.1 Types of C,P-Carbon-Substituted Phosphorus Ylides

The reactivity of phosphorus ylides depends first of all on substituents R^1 and R^2 at the ylidic carbon atom. In general, ylides with electron-withdrawing substituents R^1 and R^2 are of low nucleophilicity to carbonyl compounds. The nature of the substituents on the phosphorus atom also affects the reactivity of an ylide, although to a lesser extent. Replacement of the phenyl groups on phosphorus by electron-releasing groups, e.g. alkyl, will increase the reactivity of the ylide by stabilizing the contribution of the dipolar form in the resonance hybrid.

$$Ph_3P{=}CR^1R^2 \longleftrightarrow Ph_3\overset{+}{P}\text{-}\overset{-}{C}R^1R^2$$

In view of the large variation in their reactivity, C,P-carbon-substituted phosphorus ylides can be classified according to the substituents on the *a* carbon atom (Scheme 2.1). The simplest representatives of C,P-carbon-substituted phosphorus ylides are *phosphonium methylides* **1**. The replacement of the hydrogen atoms on the ylidic carbon atom with other substituents enables the preparation of other types of the phosphorus ylide.

Phosphonium alkylides **2,3**, bearing one or two alkyl groups on the α-carbon atom, can be termed non-stabilized; because of electron-donating properties of the alkyl groups they are highly basic and nucleophilic. The next type of phosphorus ylide is the *phosphonium arylmethylides*, **4,5**, with different aromatic substituents on the ylidic carbon atom. These ylides are semistabilized, or ylides with moderate activity. Aromatic groups delocalize the negative charge of the ylidic carbon atom, therefore phosphonium arylmethylides are of moderate basicity and nucleophilicity compared with non-stabilized ylides. They are, however, more active than stabilized ylides.. The second important type of semistabilized P-ylide is the *phosphonium allylides*. The allylic group delocalizes the negative charge of ylidic carbanion in *allylides* **6**, **7**.



Scheme 2.1

Phosphonium aldehydoylides **8** *and phosphonium ketoylides* **9**, contain a C=O group on the α-carbon, the effectively delocalizes the negative charge of the ylidic carbanion. They are of lower basicity and nucleophilicity than other types of phosphorus ylide. The electronegative oxygen atom accepts most of the negative charge of the ylidic carbon atom; as a result the ketoylide group is strongly enolized (structures **10**). *Cyclic phosphorus ylides* **11–16** are of considerable interest from the points of view of their synthesis and structure. There are two types of cyclic phosphorus ylide, *exocyclic* **11**–

13 and *endocyclic* **14–16**. Phosphorus ylides with an endocyclic P=C group are interesting theoretically, but are not applied as reagents. There are general articles describing in detail the synthesis and properties of endocyclic phosphorus ylides[2]. Phosphorus ylides containing an exocyclic P=C bond are widely used in organic synthesis. The chemical activity of exocyclic ylides depends on the ability of the cyclic system to delocalize the negative charge of ylidic carbanion. Certain types of *endo*- and *exo*cyclic phosphorus ylide are presented in Scheme 2.1.

2.2 Preparation

This chapter reviews methods available for the preparation of phosphonium ylides. Because C,P-carbon-substituted ylides are widely used in synthetic organic chemistry, the various methods available for their preparation have been studied intensively. The most general method is the preparation of a phosphonium salt and then removal of an *a* proton with a base to form the ylide; this is represented by an acid–base equilibrium (Eq. 2.1)[3b,c].

$$Ph_3P^+\text{-CHRR']X} \underset{+HX}{\overset{-HX}{\rightleftharpoons}} Ph_3P{=}CRR \tag{2.1}$$

This method can be used to prepare ylides containing different substituents at the ylidic carbon and phosphorus atoms. Various modifications of the salt method are possible (in homogenous and heterogeneous media, on polymeric supports, by electrolysis of the phosphonium salts, by elimination of trimethylchlorosilane from C-silyl-substituted phosphonium salts and so on). Of these, the method for preparation of complex ylides from simple ylides by replacement of the hydrogen atoms on the *a* carbon by different substituents has found important preparative application. This is based on the process of transylidation ("Umylidierung") observed by Bestmann,[3b,c] who converted one ylide to another by in an acid–base reaction. In addition to these direct methods, many phosphonium ylides of complex structure are best prepared from simpler ylides by their reaction with electrophiles. For example, disubstituted ylides can often be prepared from monosubstituted ylides. There are powerful alternatives to the direct synthesis of disubstituted ylides described in this chapter. Other methods for the synthesis of ylides are, as a rule, of theoretical interest only.

2.2.1 Synthesis from Phosphonium Salts

The 'salt method' for the formation of ylides involves two distinct steps: the formation of the phosphonium salt and the deprotonation of the latter to form the ylide. These are discussed separately in the first five subsections, each of which identifies essential limitations and cautions. The first subsection also describes some specialized aspects of the salt method, including 'salt-free' ylides, the instant ylide method, the electrochemical method, sonochemistry, and so on.

2.2.1.1 Dehydrohalogenation of Phosphonium Salts

The most general method for the synthesis of phosphorus ylides is the dehydrohalogenation of corresponding phosphonium salts by bases. In 1894 Mikhaelis and Gimborn[4] obtained phosphorus ylides for the first time by this method. The carbomethoxymethyltriphenylphosphonium salt was obtained by quaternization of triphenylphosphine with the ethyl chloroacetate; this was then transformed into the ylide by treatment with an aqueous solution of potassium hydroxide. The method for the synthesis of ylides from phosphonium salts is preparatively simple and with the correct choice of reaction conditions, the base, and the solvent proceeds smoothly. Ylides prepared from phosphonium salts can be introduced into the Wittig reaction and other transformation without isolation and purification—treatment of a carbonyl compound with the ylide solution can be used to prepare alkenes. Many examples have been described of the application of phosphorus ylides, prepared from phosphonium salts, for the synthesis of substances of different structure, including substances of natural origin.[4] The most important aspects of the preparation of phosphorus ylides by the salt method is the preparation of the phosphonium salt and the choice of suitable base capable of deprotonating the salt.

The usual method for the preparation of quaternary phosphonium salts is the reaction of tertiary phosphine with an electrophilic reagent, most often an alkyl halide (Eq. 2.2, Table 2.1):

$$R^1{}_3P + BrCHR^2R^3 \longrightarrow [R^1{}_3P^+CHR^2R^3]Br^- \xrightarrow[\text{Solvent}]{\text{Base}} R^1{}_3P{=}C\,R^2R^3 \qquad (2.2)$$

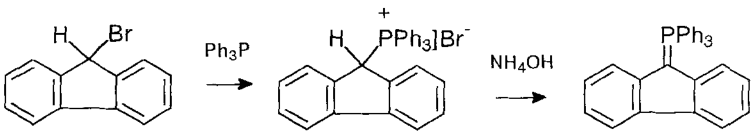
There are general articles which describe in detail various routes of approach to the phosphonium salts, which are now very accessible compounds.[5] Therefore phosphonium salts with various structures, and then phosphorus ylides, can be synthesized by this method.

The conversion of a phosphonium salt to a phosphorus ylide is performed in a solvent using a base of the appropriate strength. Different solvents—DMSO[6-11], DMFA[12], ethyl alcohol[13,14], water[15,16], benzene[17,18], diethyl ether[19,20], monoglyme, [21] diglyme, etc., can be used for the preparation of phosphorus ylides from phosphonium salts (Table 2.1)[22]. The solvent must react neither with the base nor the ylide. The nature of a solvent is not very important in the step in which the ylide is prepared from the phosphonium salt, although it must be inert to the phosphorus ylide—it is necessary to remember that non-stabilized ylides react readily with such solvents as water, alcohol, acetone, chloroform (sometimes), carbon tetrachloride, and DMFA. In the Wittig reaction step, however, the nature of the solvent is very important, because it influences the stereochemistry of olefins (see Chapter 6, Sec. 6.2.4.1). It was found that the highest Z-stereoselectivity was easily achieved by use of polar aprotic solvents[23-25] or techniques in which soluble inorganic salts were not present (lithium salt-free conditions)[23,26,27] or by use of instant ylides.

Table 2.1. Deprotonation of phosphonium salts (Eq. 2.1)

R^1	CR^2R^3	Base	Solvent	Ref
Ph	CH_2; CHAlk	KH	Et_2O, THF	46
Alk, Ph	CHAlk, CH_2	NaH	THF	48
Ph	CHAlk	NaH	DMF	49,50
Ph	CHAlk	NaH	DMSO	27
Ph	CHAlk	NaH	benzene	49,21
Ph	CHAlk	KNH_2	NH_3,THF	21 51
Alk, Ph	CHAlk	$NaNH_2$	NH_3, THF, benzene	21,27,33,42, 49,51
Ph	CHAlk	$LiN(SiMe_3)_2$	THF	52
Ph	CHAlk	$NaN(SiMe_3)_2$	THF, benzene, hexane, toluene	27,53,54,55
Ph	CHAlk	$KN(SiMe_3)_2$	THF	54,56
Ph	CHAlk	Et_2NLi	THF	35,36
Ph	CHAlk	i-Pr_2NLi	THF	37
Ph	CHAlk	K + $(Me_2N)_3PO$	hexamethapol	57
Ph	CHAlk	t-BuOK	THF	49,58-60
Ph	CHAlk	BuLi	Et_2O, benzene,THF	49, 61 62
Ph	CHAlk	PhLi	Et_2O,THF	63
Ph	CHAlk	$NaCH_2SOMe$	DMSO	64
			hexametapol	57
Ph	CHAlk	NaOMe	DMF	65
Ph	CHAlk	$Me_3P{=}CH_2$	ether	48
Ph	CHAr	AlkOM,M= Li, Na, K	AlkOH, Alk=Me, Et	66,67
Ph	CHAr	EtOLi	EtOH, DMF	66a
Ph	CHAr	$NaN(SiMe_3)_2$	THF	27
Ph	CHAr	$H_2N(CH_2)_3NHLi$	THF, hexametapol	41
Ph	CHAr	NaOH	H_2O/CH_2Cl_2	68
Ph	CHAr	NaH	DMF	50b
Ph	CHAr	BuLi	benzene, THF	62b
Ph	CAr_2	NH_3	EtOH, H_2O	28
Ph	CHCH=CHR	NaH	DMF, DMSO	50
Ph	CHCH=CHR	$NaNH_2$	NH_3	69
Ph	CHCH=CHR	$LiNEt_2$	THF	36
Ph	CHCH=CHR	ROLi, RONa	ROH, R=Me, Et, t-Bu	70
Ph	CHCH=CHR	$NaN(SiMe_3)_2$	THF	71
Alk, Ph	CHAlk	MeLi	diethyl ether	31,72
Ph	C(O)R, R=Ar, Alk, OAlk, OAr	Na_2CO_3	H_2O, benzene, *methanol*	29,31,72
Ph	C(O)R,	K_2CO_3	H_2O	73
Ph	CO_2Et	NaOEt	Ethanol	13,14
Ph	C(O)R	Et_3N	CH_2Cl_2, C_2H_5OH	30,31,74
Ph	CN	NaOH, KOH, LiOH	H_2O	16,29,35,75,76
Ph	CN	Et_3N	CH_2Cl_2,	30,31
Ph	CN	Pyridine	CH_2Cl_2, CH_3NO_2	29
Ph	CN	DBN, DBU	DMSO	32

The selection of a suitable base is important in the preparation of phosphorus ylides from phosphonium salts. The strength of the base required for the deprotonation of phosphonium salts depends on the CH-acidity of the hydrogen on the α carbon atom. Thus, phosphonium salts bearing electron-withdrawing groups on the α carbon atom, the precursors to stable ylides, are easily deprotonated with dilute aqueous alkalis or neat amines. If there are electron-donating substituents on the α carbon, for example alkyl groups, then alkyl-metals or hydrides are normally required to remove the α proton. Intermediate between these two extremes is when the α proton is allylic or benzylic, then alcoholic alkoxide is the base of choice. Any substituents on the α phenyl group will, of course, modify the acidity of the proton by their electronic effects. The CH-acidity of phosphonium salts depends on the electron-accepting properties of substituents R^1 and R^2. Electron-withdrawing groups, capable of accepting part of the negative charge via inductive or mesomeric effects, must stabilize the phosphorus ylide, reducing the basicity and nucleophilicity of the ylidic carbon atom, and, accordingly, raising CH-acidity of the phosphonium salts. Relatively weak bases can be uses for phosphonium salts with highly mobile protons. For instance, fluorenyltriphenylphosphonium bromide was converted into ylide (II) by the action of an aqueous solution of ammonia (Eq. 2.3)[28].



(2.3)

Preparation of triphenylphosphonium fluorenylide (Eq. 2.3) [28]

a) A solution of 9-bromofluorene (3 g) in nitromethane (approx. 40 mL) was placed in a reaction vessel and a solution of triphenylphosphine (3.21 g) in nitromethane was added dropwise at +10°C. The reaction is exothermic, as evidenced by a 10° rise in the temperature of the solution. After 2 h stirring at room temperature the fluorentriphenylphosphonium bromide (5.75 g), mp 303°C, was removed by filtration.

b) The prepared bromide (3 g) was dissolved in boiling alcohol (150 mL) and treated with aqueous ammonia (approx. 8 mL). Yellow-glistening plates crystallized as the solution cooled. Yield 2.4 g, mp 253°C.

Deprotonation of phosphonium salts with highly mobile α protons can be achieved with organic bases (pyridine,[29] triethylamine[30,31]). DBN[32a] and DBU[32b] have been proposed for the dehydrohalogenation of phosphonium salts in the Wittig reaction with aldehydes sensitive to alkalis (dienes, vitamin A acetate). DMSO has been used as solvent for the preparation of P-ylides (Eq. 2.4):[32]

$$[Ph_3P^+CH_2R]Cl^- \xrightarrow{\text{DBN/DMSO}} Ph_3P{=}CHR \xrightarrow[-Ph_3PO]{PhCHO} PhCH{=}CHR \qquad (2.4)$$

$$R = -C(CH_3){=}CHCO_2Me,\ CO_2CH_3$$

Sodium and potassium amides,[33,34] lithium diethylamide,[35,36] lithium diisopropylamide,[37] lithium piperidide,[38] lithium, potassium and sodium bis(trimethylsilyl) amides[39,40] are used more often than alkylamines and ammonia for the dehydrohalogenation of phosphonium salts.

Lithium 1,3-diaminopropane is a very active deprotonating reactant for the preparation of non-stabilized ylides from alkyltriphenylphosphonium salts.[41] These strong bases readily deprotonate different phosphonium salts and are applied with success for the preparation of the ylides of various structures.

Sodium amide and, particularly, sodium bis(trimethylsilyl)amide have proved very good for the generation of salt-free ylides from the corresponding phosphonium salts. Sodium bis(trimethylsilyl)amide has the advantage of being easy to handle and to dispense, and soluble in many solvents (Eq. 2.5):[27]

$$[Ph_3P^+CH_2Et]Br^- \xrightarrow[-NaBr]{NaN(SiMe_3)_2} Ph_3P{=}CHEt \qquad (2.5)$$

The deprotonation of phosphonium salts with sodium amide can be performed in liquid ammonia, in which it was prepared directly, or in organic solvents with previously prepared, solid, sodium amide. Sodium amide can also be used in the form of a suspension in mineral oil—powdered sodium amide coated with paraffin is mixed with powdered phosphonium salt to form a storable dry mix which upon addition of ether or tetrahydrofuran affords a solution of ylide that can be used for various reactions. For example, reaction of trimethyl-*tert*-butylphosphonium bromide with a suspension of sodium amide in THF for 3 h at room temperature results in *tert*-butyldimethylphosphonium methylide in 42% yield. Dimethyl-di-*tert*-butylphosphonium bromide is converted to the ylide by reaction with sodium amide under reflux in THF for 3 h. The sterically hindered tri-*tert*-butylmethylphosphonium bromide was deprotonated with liquid ammonia at −40°C (Eq. 2.6)[42]:

$$[Me_{n+1}P(Bu\text{-}t)_{3-n}]^+Br^- \xrightarrow[-NH_3,\ -NaBr]{NaNH_2/NH_3} Me_n(Bu\text{-}t)_{3-n}P{=}CH_2 \qquad (2.6)$$

$n=0,1,2$

Preparation of di-tert-butylmethylphosphonium methylide (Eq. 2.6)[42]

A suspension of sodium amide (1.3 g, 0.05 mmol) and di-*tert*-butyldimethyl-phosphonium bromide (2.2 g, 0.057 mmol) in tetrahydrofuran (100 mL) was heated under reflux with stirring for 3 h. The sodium bromide was separated, the solvent was removed under reduced pressure, and the residue was distilled in vacuo. Yield 6.1 g (67%), bp 102–104°C (8 mm Hg).

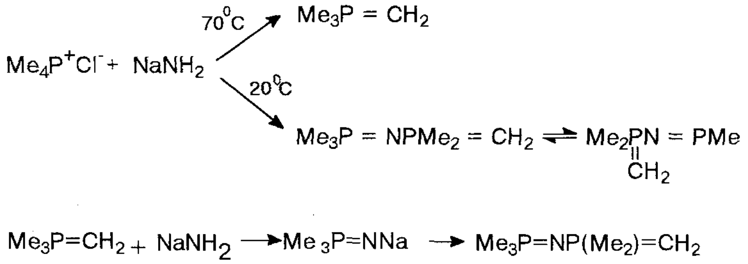
A useful perfection of the salt method are the *instant ylidic mixtures* proposed by Schlosser and Schaub[43–47]. The instant ylide method relies on the surprising inertness of sodium amide (pK_a ammonia ~40) towards phosphonium salts (pK_a ~20) as long as the two components are mixed in the form of dry powders. Upon addition of an ethereal solvent, however, the ylide is quantitatively generated after a few minutes stirring (Eq. 2.7). A mixture of potassium hydride and powdered alkyltriphenylphosphonium salts are ready to use and are well preserved in a closed flask (6 months at 0°C). The preparation of these mixtures can be easily performed on ordinary balances.

$$[Ph_3P^+CH_3R]X + KH \longrightarrow Ph_3P{=}CHR$$

$$R{=}Me,\ CH_2F,\ CH_2OMe,\ NC_5H_4CH_2CH_2.\ X{=}Br,\ Cl,\ BF_4 \qquad (2.7)$$

Instant ylidic mixtures are very convenient for the olefination of carbonyl compounds in the Wittig reaction (Chapter 6, Section 6.2.1).[43–47]

Sometimes the reaction of phosphonium salts with sodium amide is accompanied with complications.[33] For example, the dehydrochlorination of tetramethylphosphonium chloride with sodium amide in boiled tetrahydrofuran proceeds smoothly to result in trimethylphosphonium methylide (Scheme 2.2).



$$Me_4P^+Cl^- + NaNH_2 \xrightarrow{70^0C} Me_3P = CH_2$$

$$Me_4P^+Cl^- + NaNH_2 \xrightarrow{20^0C} Me_3P = NPMe_2 = CH_2 \rightleftharpoons Me_2\underset{\overset{\|}{CH_2}}{P}N = PMe$$

$$Me_3P{=}CH_2 + NaNH_2 \longrightarrow Me_3P{=}NNa \longrightarrow Me_3P{=}NP(Me_2){=}CH_2$$

Scheme 2.2

Triphenylphosphonium alkoxycarbonylmethylides and the triphenylphosphonium β-ketoylides have been prepared by treatment of phosphonium salts with an aqueous or alcoholic solution of sodium carbonate (Eq. 2.9)[73,77], or sodium or potassium hydroxide (Eq. 2.8; 2.10):[16,29]

$$Ph_3P + BrCH_2CO_2Et \longrightarrow [Ph_3\overset{+}{P}CH_2CO_2Et]\,Br^- \xrightarrow[H_2O]{NaOH} Ph_3P{=}CHCO_2Et \qquad (6.8)$$

$$Ph_3P + BrCH_2C(O)R \longrightarrow [Ph_3\overset{+}{P}CH_2C(O)R]\,Br^- \xrightarrow[H_2O]{Na_2CO_3} Ph_3P{=}CHC(O)R \qquad (6.9)$$

$$Ph_3P + BrCH_2COSMe \longrightarrow [Ph_3\overset{+}{P}CH_2COSMe]\,Br^- \xrightarrow[H_2O]{NaOH} Ph_3P{=}CHCOSMe \qquad (6.10)$$

Preparation of triphenylphosphonium carbethoxymethylide (Eq. 2.8)[29,35]

a) Carbethoxymethyltriphenylphosphonium bromide was prepared by treating a solution of triphenylphosphine (157 g, 0.6 mol) in benzene (300 mL) with ethyl bromoacetate (100 g, 0.6 mol) in benzene (300 mL) at room temperature. The phosphonium salt began precipitating immediately and the temperature reached *ca* 70°C within a few minutes. The mixture was shaken vigorously and left to stand overnight. The solid was removed by filtration, washed with benzene and pentane, and dried.

b) The salt was dissolved in water (1500 mL) and benzene (1000 mL) was added. The stirred mixture was adjusted to the phenolphthalein end-point by addition of aqueous sodium hydroxide and the two layers were separated. The benzene layer was dried and concentrated under vacuum. Careful addition of petroleum ether (30–60°C) caused crystallization of the ylide. The ylide was removed by filtration and dried. Yield 159 g (76%), mp 125–127.5°C.

Preparation of triphenylphosphonium acetylmethylide (Eq. 2.9)[31,72]

a) A solution of triphenylphosphine (10.06 g) and chloroacetone (3.25 g) in chloroform was heated under reflux for 45 min. The reaction solution was removed by filtration mixed with anhydrous ether (300 mL), and the acetonyltriphenylphosphine chloride was collected. Yield 11.2g, mp 234–237°C.

b) A mixture of acetonyltriphenylphosphonium chloride (13 g) and 10% aqueous sodium carbonate was stirred for 8 h. The solid was removed by filtration and dried. Yield 1.07 g, mp 199–202°C

Preparation of triphenylphosphonium benzoylmethylide (Eq. 2.9)[31,72]

a) Phenacyl bromide (8.35 g) was added slowly to a solution of triphenylphosphine (10.89 g) in chloroform (75 mL). The reaction solution was mixed with anhydrous ether (1 L) and the precipitate was collected and dried. Yield 15 g, mp 267–269°C.

b) A mixture of phenacyltriphenylphosphonium bromide (7.5 g) and aqueous sodium carbonate (10%, 300 mL) was stirred for overnight. The reaction mixture was filtered and the insoluble portion was taken up in hot benzene (200 mL). Some unreacted phosphonium salt was removed by filtration. Petroleum ether was added to filtrate and the solid formed was isolated by filtration. Yield 5.8 g, mp 178–180°C (after recrystallization 200.5–202.5°C).

Preparation of triphenylphosphonium carbomethylthiomethylide (Eq. 2.10)[76]

a) Thiomethyl α–bromoacetate (112 g, 0.67 mol) was slowly added to a solution of triphenylphosphine (175 g, 0.67 mol) in absolute benzene (60 mL). After addition the reaction mixture was stirred at room temperature for 6 h and then left to stand overnight. The precipitate formed was collected and washed with absolute benzene to give the phosphorus ylide which was recrystallized from methanol–ether.

b) A suspension of carbomethylthiomethyltriphenylphosphonium bromide (43 g, 0.1 mol) in water (800 mL) was stirred at room temperature while a solution of sodium hydroxide (5%, 80 mL) was slowly added. After addition the reaction mixture was further stirred at room temperature for 30 min. The precipitate formed was removed by filtration, washed with ice-cold water until neutral and dried over P_2O_5 under vacuum to give desired product, which was recrystallized from chloroform–ethyl acetate. Yield 34.5 g (98%), mp 170°C (dec.)

The conversion of phosphonium salts with low CH-acidity into ylides, for instance for the preparation of triphenylphosphonium methylide or triphenylphosphonium alkylides, can be performed with sodium or potassium hydrides, [48,80] which enable the preparation of salt-free phosphorus ylides in aprotic solvents. The sodium and potassium hydrides are used in diethyl ether, tetrahydrofuran or dimethoxyethane as

solvents. The sodium hydride is recommended as a base if dimethylformamide is used as solvent. The deprotonating activity increases substantially in the sequence:
ether < THF < DME.
The reaction of methyltriphenylphosphonium bromide with the sodium hydride in THF leads to the formation of the triphenylphosphonium methylide of high purity (Eq. 2.11)[48]:

$$[Ph_3PMe]^+ Br^- + NaH \longrightarrow Ph_3P{=}CH_2 \qquad (2.11)$$

Preparation of triphenylphosphonium methylide (Eq. 2.11)[48]
Methyltriphenylphosphonium bromide (29.0 g, 0.081 mol) was added to a suspension of sodium hydride (1.67 g) in tetrahydrofuran (200 mL). The reaction mixture was stirred for 24 h at room temperature, the precipitate of NaBr was removed by filtration, and the solvent was removed under vacuum. The ylide was extracted from the residue with petrol ether (40–60°C). The ylide, mp 96°C, was obtained after crystallization. Yield 6.0 g (82%). All operations must be performed under argon.

Preparation of triphenylphosphonium bis(p-methoxyphenyl)methylide[346]
The bis(methoxyphenyl)methyltriphenylphosphonium bromide (11.5 g, 20 mmol) was dissolved in toluene–THF (2:1, 300 mL). Sodium amide (0.79 g, 20 mmol) was added and the mixture was stirred at ambient temperature for 15 h. Argon was passed through solution for 10 min. The precipitated sodium was stripped in vacuo to give the ylide as a light red solid. Yield 8.8 g (85%), mp 102°C.

A solution of sodium hydride in dimethyl sulfoxide (dimsyl sodium) was proposed by Corey and Chaykowsky[7,8,64] as a convenient dehalogenating reagent. They found that sodium hydride reacts readily with dimethyl sulfoxide to form sodium methylsulfinylmethanide which dehydrohalogenates phosphonium, sulfonium, sulfoxonium, and arsonium salts under mild conditions. This extremely reactive compound can be obtained by reaction of excess DMSO with the sodium hydride suspension under an inert atmosphere at 65–70°C (Eq. 2.12). Solutions containing this anion have generally been prepared by heating a suspension of sodium hydride in dimethyl sulfoxide at 70°C for 1 h. Such solutions are sensitive to heat and air and decompose rapidly above 85°C. Dimsyl sodium reacts at room temperature with ethyl- and methyltriphenylphosphonium bromides (Eq. 2.13) to afford solutions of the corresponding phosphorus ylides, which olefinate various aldehydes and ketones in high yields. Corey and Chaykovsky[64] proposed a method for the preparation of phosphorus ylides with dimsyl sodium:

$$CH_3S(O)CH_3 + NaH \longrightarrow [CH_3S(O)CH_2]^-Na^+ \qquad (2.12)$$

$$[Ph_3PMe]^+Br^- + [CH_3S(O)CH_2] Na^+ \longrightarrow Ph_3P{=}CH_2 \qquad (2.13)$$

Preparation of triphenylphosphonium methylide (Eq. 2.13)[64]
Sodium hydride (0.1 mol, as a 55% suspension in mineral oil) was washed with several portions of pentane and placed in a three-necked flask equipped with stirrer, reflux condenser and rubber septum-seal. The reaction system was flushed with nitrogen, and DMSO (50 mL) was introduced by syringe via the rubber seal. The mixture was heated to

75–80°C for 45 min up to the termination of evolution of hydrogen. The prepared solution of sodium methylsulfonyl methylide was cooled to 0°C and a solution of methyltriphenylphosphonium bromide (35.7 g, 0.1 mol) in DMSO (100 mL) was added. A dark-red solution of the ylide was obtained after the stirring of reaction mixture at room temperature for 10 min. The prepared solution of ylide olefinates cyclohexanone, camphor, and cholestanone-3, converting them to the methylene compounds in yields of 86, 73 and 60%, respectively.[64]

Because dimsyl sodium prepared by the Corey and Chaykovsky method is not sufficiently stable the preparation of dimsyl sodium solutions was perfected. Sjoberg proposed ultrasound treatment of DMSO containing a 50% suspension of sodium hydride in mineral oil. The prepared solution of dimsyl sodium covered with the layer of mineral oil can be stored under refrigeration for 2 months[82]. Solutions of phosphorus ylides in DMSO prepared in this manner are suitable for the preparation of low-boiling hydrocarbons, which can be easily distilled from high-boiling solvent.

Preparation of a stable solution of sodium methylsulfinylmethanide[82]

A 50% suspension of sodium hydride in mineral oil (15 g) was stirred into dry dimethyl sulfoxide (200 mL) and with continuous stirring treated with ultrasound. The temperature rose to 50°C and a fine very reactive dispersion resulted, which in 1 h yielded a clear solution of sodium methylsulfinylmethanide. The solution was protected against air by a 1-cm surface layer of mineral oil. The required amount of reagent can be withdrawn from the stock solution by means of a pipet. At ca 10°C the reagent solidifies and can be stored for 2 months.

Occasionally the blue solutions of alkali metals in the hexamethyltriamide of phosphorous acid (hexametapol) are used with success for dihydrohalogenation of phosphonium salts and for their transformation into ylides (Scheme 2.3)[57]. Fraenkel and coworkers[83] found, that sodium, potassium and lithium dissolve in hexametapol to give blue solutions with concentrations up to 1 M which are stable for several hours, On introduction of oxygen to these solutions the blue color disappears and after several hours of storage at room temperature the solutions turn red.

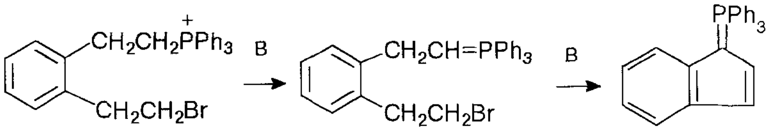
$$(Me_2N)_3P{=}O + 2K \longrightarrow (Me_2N)_2PO^- + Me_2N^- + 2K^+$$

$$[Ph_3PCH_2R]^+Br^- \xrightarrow{(Me_2N)_3P=O\ +\ Me_2N^-} Ph_3P{=}CHR$$

R=Me, Et, Pr, Bu, Ph

Scheme 2.3

Bestmann obtained cyclic ylides by the action of potassium on a suspension of 2-(2-bromoethyl)benzyltriphenylphosphonium bromide in hexametapol (Eq. 2.14)[57]: Non-stabilized phosphorus ylides such as trimethyl- and triphenylphosphonium methylides are very strong bases and good dehydrohalogenating reagents.



(2.14)

B = 2K + $(Me_2N)_3P{=}O$

Although these reagents more expensive than other bases used for preparation of ylides, they enable the smooth deprotonation of phosphonium salts (Eq. 2.15, 16). They are quite well soluble in non-polar organic solvents, and can be easily isolated from the reaction mixture because the solids are insoluble after addition of hydrogen halide.

$$[Ph_3PMe]^+Br^- \xrightarrow[-b]{a} Ph_3P{=}CH_2 \tag{2.15}$$

$$[Ph_3PCH_2Ph]^+Br^- \xrightarrow[-b]{a} Ph_3P{=}CHPh \tag{2.16}$$

a= $Me_3P{=}CH_2$; b= Me_4PCl

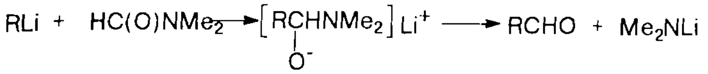
Alkyl- and aryllithiums – *e.g.* *tert*-butyllithium, *sec*-butyllithium, *n*-butyllithium,[18-20,49] phenyllithium,[84] and methyllithium,[85] are used as bases for the preparation of phosphorus ylides (Eq. 2.17). These reagents have high dehydrohalogenating capacity and readily deprotonate different phosphonium salts (pK_a of lithium alkyls are ~45–35, pK_a of phosphonium salts are <20). Organolithium compounds are accessible, easily stored for several weeks or months (especially butyllithium, phenyllithium, methyllithium), and can be easily dispensed by means of a pipet. Alkyllithiums are especially convenient for performing the Wittig reaction without isolation of ylides from reaction solutions:

$$[Bu_4P]^+Br^- \xrightarrow[-LiBr]{BuLi} Bu_3P{=}CHPr \tag{2.17}$$

Preparation of tributylphosphonium butylide (Eq. 2.17)[62]

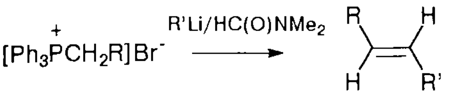
A solution of tetrabutylphosphonium bromide (6.8 g, 20 mmol) in absolute THF (60 mL) was placed in a flask under nitrogen and a solution of *n*-butyllithium in hexane (13.0 mL, 1 N) was added dropwise to the reaction mixture with stirring, at 0°C. The reaction mixture was stirred at this temperature for 15 min, and the solvent was then removed under reduced pressure and the residue was distilled under vacuum (p = 0.1 mmHg) in a Kugelrohr apparatus at a pot temperature of 110°C. A pale air-sensitive liquid (4.15 g, 80%) containing 95% of the desired ylide (δ_P 8.7 ppm) was obtained (5% Bu_3P was detected by NMR, δ_P 40.8 ppm).

Organolithium compounds cannot be used with DMFA as solvent, because they react to form aldehydes, which undergo the Wittig reaction (Eq. 2.18).[86,87] A novel synthesis has recently been provided by the reaction of phosphonium salts with organolithium reagents in DMF. The reaction, which usually gives excellent yields, presumably proceeds via the initial formation of an aldehyde by reaction of the organolithium reagent with DMF (Eq. 2.19)[88]:



$$RLi + HC(O)NMe_2 \longrightarrow [R\underset{O^-}{\underset{|}{C}}HNMe_2]Li^+ \longrightarrow RCHO + Me_2NLi$$

(2.18)



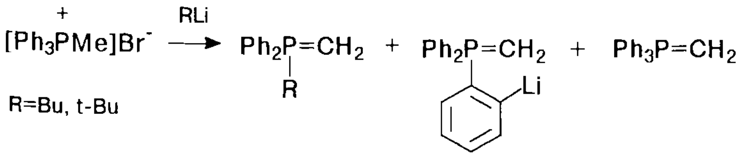
(2.19)

Sodium hydride does not react with DMFA and can be used as a base in this solvent (Eq. 2.20)[50]:

$$[Ph_3P^+CH_2CH{=}CHR]X^- \xrightarrow{NaH/DMF} Ph_3P{=}CHCH{=}CHR \tag{2.20}$$

The choice of base might be affected by factors other than the acidity of the *a* hydrogen, e.g. the presence of functionality in the phosphonium salt. The nature of the base and the nature of the anion of the phosphonium salt, are very important, because ylides form stable complexes with alkali metals; these react with carbonyl compounds with different stereoselectivity than salt-free phosphorus ylides. Such complexes are formed during the dehydrohalogenation of the phosphonium salt with alkyllithiums. To prepare salt-free ylides it is necessary, to remove the lithium, sodium or potassium chlorides from the reaction solutions. Sodium amide[21] and sodium bis(trimethylsilyl) amide[27] are convenient bases for the preparation of salt-free ylides.

Various methods have been developed for the preparation of salt-free ylides. Thus, ylides were obtained in anhydrous ammonia by means of sodium amide and then transferred into benzene solution[21]. A variant of this method is the reaction between phosphonium salts and sodium amide in boiled THF with subsequent filtration of the sodium halide[51]. Good results were obtained with the potassium *tert*-butoxide[49] and sodium bis(trimethylsilyl)amide in THF.[27] The dehydrohalogenation of phosphonium salts proceeds smoothly with sodium *tert*-pentoxide dissolved in benzene containing DMSO.[22] In recent years crown ethers and potassium carbonate or potassium *tert*-butoxide in THF have been used for the preparation of salt-free ylides[89]. Treatment of phosphonium salts with lithium alkyls is followed by ligand exchange (Eq. 2.21):[90]



(2.21)

Schlosser and coworkers showed by low-temperature NMR that the reaction of methyltriphenylphosphonium bromide with alkyllithiums leads to the formation of an ylide lithiated in the benzene ring and an ylide formed as a result of substitution of a phenyl group on the phosphorus atom by an alkyl group (Eq. 2.21). The ratio of these ylides depends on the nature of the lithiumalkyl[91].

Seyferth and coworkers[92,93] found that reaction of methyl triphenylphosphonium bromide with methyllithium leads to the formation of the pentavalent intermediate which decomposes to form phenyl anion and triphenylphosphonium salt, resulting in the diphenylmethylphosphonium methylide (Eq. 2.22,23). Reaction of tetraphenylphosphonium bromide with methyllithium gives triphenylphosphonium methylide (Eq. 2.23); this undergoes the Wittig reaction with cyclohexanone to result in methylenecyclo-hexanone in 58% yield:

$$[Ph_3PMe]^+Br^- \xrightarrow{a} Ph_3PMe_2 \rightarrow Ph_2P^+Me_2 + C_6H_5^- \xrightarrow[-C_6H_6]{} Ph_2P(Me){=}CH_2 + C_6H_6 \quad (2.22)$$

$$[Ph_4P]^+Br^- \xrightarrow{a} Ph_4PMe + C_6H_5 \longrightarrow Ph_3P{=}CH_2 + C_6H_6 \quad (2.23)$$

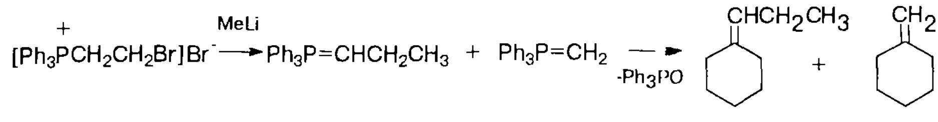
a = MeLi

The deprotonation of the haloalkylphosphonium salts with butyl and phenyllithium is accompanied by exchange of the halogen atoms on the α carbon for lithium or a butyl group, giving rise to a mixture of ylides. The tendency of the triphenylphosphonium halomethylides to react with organolithium compounds increases in the sequence Cl < Br < I. Phosphonium salts bearing halogen on the α carbon atom, undergo attack with alkyllithium both at the proton and at the halogen atom to produce products in a ratio which depends on nature of halogen and base used. Bromo- and iodomethyltriphenylphosphonium bromides with phenyllithium produce ylides **19**,**20**, which enter into a Wittig reaction with cyclohexanone (Eq. 2.24)[93,94]. The bromoethylphosphonium salt **21** reacts with phenyllithium to afford the vinylphosphonium salt **22**, which reacts with excess phenyllithium to produce 2-phenylethylide (Eq. 2.26)[95]:

$$[Ph_3PCH_2X]^+X^- \longrightarrow \underset{\mathbf{19}}{Ph_3P{=}CH_2} + \underset{\mathbf{20}}{Ph_3P{=}CHX} \quad (2.24)$$

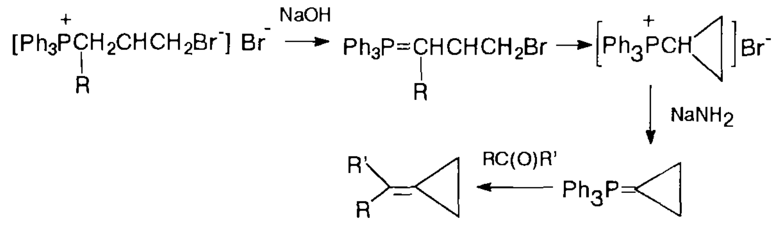
$$\underset{\mathbf{21}}{\overset{+}{[Ph_3PCH_2CH_2Br]}Br^-} \xrightarrow{PhLi} \underset{\mathbf{22}}{\overset{+}{[Ph_3PCH{=}CH_2]}Br^-} \xrightarrow{PhLi} Ph_3P{=}CHCH_2Ph \quad (2.25)$$

Reaction of β-bromoethyltriphenylphosphonium bromide with methyllithium furnishes a mixture of triphenylphosphonium propylide and triphenylphosphonium methylide because of exchange of ligands; these ylides react with the cyclohexanone to provide a mixture of propylenecyclohexenone and methylenecyclohexenone (Eq. 2.26).



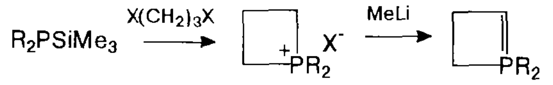
(2.26)

3-Bromopropyltriphenylphosphonium salts react with bases to furnish derivatives of cyclopropyltriphenylphosphonium bromide. In the first step the reaction affords ylides which undergo intramolecular alkylation to produce phosphonium salts. The dehydrochlorination of these salts with sodium amide affords the highly reactive triphenylphosphonium cyclopropylide, which enters into the Wittig reaction with carbonyl compounds (Scheme 2.4)[96,97,368]:



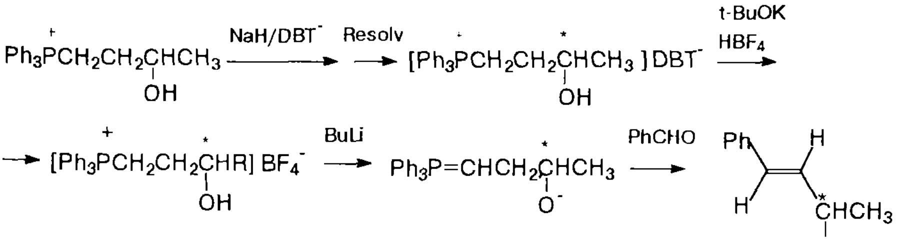
Scheme 2.4

A four-membered cyclic phosphonium ylide was prepared by deprotonation of corresponding phosphonium salt with methyllithium (Eq. 2.27)[98]:



(2.27)

Okuma and coworkers[99] prepared optically active 2- and 3-hydroxyalkyltriphenylphosphonium salts by optical resolution as their 2,3-*D*-*O*-benzoyltartrates. The reaction of enantiomerically pure salts with butyllithium afforded the corresponding optically active ylides (Scheme 2.5):



DBT =Dibenzoyltartrate

Scheme 2.5

2.2.1.2 Synthesis from α-Silyl- and α-Stannyl-substituted Phosphonium Salts

α-Silyl- and α-stannylsubstituted phosphonium salts readily eliminate chlorotrimethylsilane or chlorotrimethyltin to furnish phosphorus ylides. For instance, heating of trimethyltinphosphonium iodides resulted in expulsion of iodotrimethyltin and formation of the corresponding phosphorus ylides (Eq. 2.28)[100]:

$$[R_3PCH_2SnMe_3]^+I^- \longrightarrow R_3P{=}CH_2 + Me_3SnI \qquad (2.28)$$

Pyrolysis of the trimethylsilylmethyltriphenylphosphonium chloride for 2 h at 220°C affords the triphenylphosphonium methylide in 98% yield. The ylide was obtained in the crystalline form (mp 76–77°C) and introduced into the Wittig reaction with carbonyl compounds (Eq. 2.29):[101-103]

$$[Ph_3\overset{+}{P}CH_2SiMe_3]Cl^- \xrightarrow[-Me_3SiCl]{} Ph_3P{=}CH_2 \xrightarrow{R_2C=O} R_2C{=}CH_2 \qquad (2.29)$$

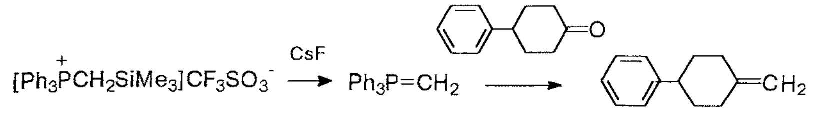
Heating trimethylsilylmethyltrimethylphosphonium chloride at 180°C under vacuum produces trimethylsilylchloride and trimethylphosphonium methylide as volatile products, distillable under vacuum, and leaves a residue of solid tetramethylphosphonium chloride (Eq. 2.30).[102] One-pot reaction of carbonyl compounds with chloromethyltrimethylsilane and triphenylphosphine leads to the formation of olefins in high yields (Eq. 2.31):[103]

$$[Ph_3\overset{+}{P}CH_2SiMe_3]Cl^- \xrightarrow[-Me_3SiCl]{} Ph_3P{=}CH_2 \xrightarrow[-Ph_3PO]{Ph_2C=O} Ph_2C{=}CH_2 \qquad (2.30)$$

$$Ph_3P + ClCH_2SiMe_3 + Ph_2C{=}O \xrightarrow[-Me_3SiCl]{t^o} Ph_2C{=}CH_2 \qquad (2.31)$$

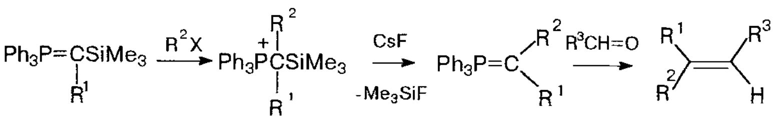
Fluoride-ion induces cleavage of the Si–C bond of silyl-substituted phosphonium salts to generate phosphorus ylides. The reaction proceeds most easily with cesium fluoride in acetonitrile owing to its high solubility in this polar organic solvent. Potassium fluoride, for instance, is considerably less soluble and even in the presence of crown ethers furnishes lower yields of phosphorus ylides.

Tetrabutylammonium fluoride readily cleaves Si–C bonds in phosphonium salts, however yields of phosphorus ylides and olefins are low. The desilylation of silyl-substituted phosphonium salts with cesium fluoride in acetonitrile proceeds smoothly and in the presence of carbonyl compounds provides good yields of olefins. Thus, the reaction of trimethylsilylmethyltriphenylphosphonium triflate with cesium fluoride in acetonitrile in the presence of 4-phenylcyclohexanone at 20°C affords 4-phenylmethylcyclohexane in 70% yield (Eq. 2.32): [104]



(2.32)

Reaction of C-silylated phosphonium salts with fluoride anion produces phosphonium ylides, which enter in situ into the Wittig reaction with aldehydes to result in olefins. This reaction has recently been proposed by Bestmann for the preparation of naturally occurring compounds, in particular for the synthesis, of homoconjugated *Lepidoptera* pheromones.[105] According to the methodology of Bestmann the reaction of an α–silylated phosphorus ylide with alkyl halides affords the alkylated α–silylphosphonium salt. Treatment of the phosphonium salt with cesium fluoride in appropriate solvent causes the desilylation with splitting of trimethylfluorosilane and the formation of the substituted ylide. The latter reacts with carbonyl compounds to provide a substituted alkene (Eq. 2.33):[105]



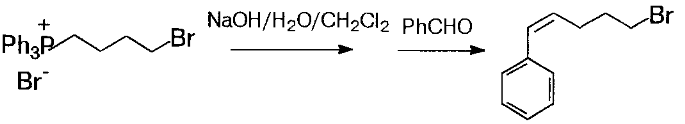
(2.33)

Examples of the application of this method for the synthesis of naturally occurring compounds are reviewed in Chapter 6.

2.2.1.3 Preparation in Heterogeneous Media

Differently improved methods have been developed for the preparation of phosphorus ylides. One is dehydrohalogenation of phosphonium salts in heterogeneous media in the presence of crown ethers, or their preparation in biphasic systems with phase-transfer catalysis.

The synthesis of phosphorus ylides under biphasic conditions eliminates the need to use strong bases such as butyllithium and sodium hydride:they can be replaced with by aqueous solutions of alkalis.[106] The generation of phosphorus ylides under biphasic conditions is widely used for the olefination of carbonyl compounds by means of the Wittig reaction[107] (Eq. 2.34). Reviews have been dedicated to the generation of phosphorus ylides in heterogeneous media[106a,b]

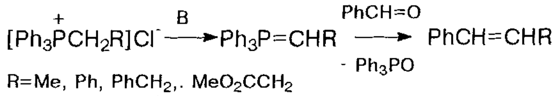


(2.34)

One significant achievement of phosphorus ylide chemistry is the synthesis of phosphorus ylides on a polymer support. Basic treatment of phosphonium salts attached to a polymer support affords polymer-based phosphorus ylides which can be introduced into various chemical transformations. The Wittig reaction with polymer-based phosphorus ylides affords solutions of alkenes of high purity and the phosphine oxides as a part of polymer, thereby facilitating separations. The phosphine oxide could be reduced to phosphine and recycled[108] (see Sec. 6.3.2.3).[109]

2.2.1.4 Electrochemical Method

An electrolytic method for the synthesis of phosphorus ylides from phosphonium salts has recently been developed[110–116]. Saveahn and Bihn[113,114] showed that electrolytic reduction of phosphonium salts under aprotic conditions led to the formation of ylides. In the presence of a small amount of water the ylide was hydrolyzed to produce phosphine oxide and hydrocarbon[114]. Phosphorus ylides prepared from benzyl-, allyl-, cinnamyl- and polyenylphosphonium salts were detected by cyclic voltametry. Later Shono and Mitani[110] and Iversen[111] reported that electrolysis with a carbon electrode in the presence of a carbonyl compound provided the Wittig reaction product (Eq. 2.35)[110]:



$$[Ph_3\overset{+}{P}CH_2R]Cl^- \xrightarrow{B} Ph_3P{=}CHR \xrightarrow[-\,Ph_3PO]{PhCH{=}O} PhCH{=}CHR \qquad (2.35)$$

R=Me, Ph, $PhCH_2$,. MeO_2CCH_2

Two-electron transfer was involved and resulted in ylide formation.[112–114] Two-electron electrochemical reduction of trichloromethyl tris(dimethylamino) phosphonium tetrafluoroborate leading to tris(dimethylamino)phosphonium dichloromethylide was developed by Collignon and coworkers.[114]

Advantages of the electrochemical method for the synthesis of the phosphorus ylides from phosphonium salts are good reproducibility of the reaction conditions, and the possibility of controlling the process and influencing the course of the reaction by variation of amperage, and by choice of the probase, the electrolytic cation, and the value of the cathode potential (Sec.6.3.2.4).

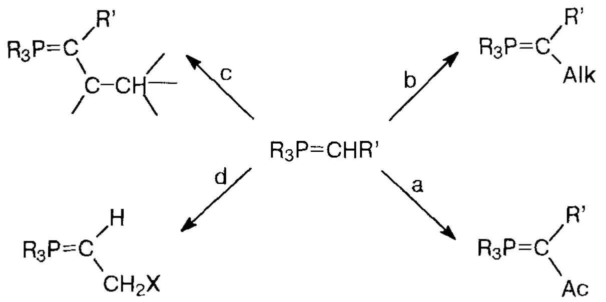
2.2.1.5 Ultrasound

Carbon–carbon bond formation is crucial in organic chemistry and it is no surprise that ultrasound has been employed to facilitate the Wittig reaction (Sec.6.2.4.4). Most recent papers have dealt with reactions that have also benefited from irradiation with ultrasound.[117] A review has been published describing the application of ultrasound in the Wittig reaction.[118]

2.2.2 Modification of Simple Phosphorus Ylides

The next important method for the synthesis of phosphorus ylides is modification of simple ylides by replacement of a hydrogen atom on the ylidic carbon atom. Because of the accessibility of simplest phosphorus ylides, this route is the most simple.

Replacement on the ylidic carbon atom is achieved by reaction of P-ylides with halogenated electrophiles or with compounds having activated multiple bond (Scheme 2.6)[119a].



a) acylation; b) alkylation; c) addition to multiple bonds; d) reaction in side chain ($R' = CH_3$)

Scheme 2.6

These reactions proceed via the formation of phosphonium salts or betaines; these lead to new ylides as a result of dehydrohalogenation or proton migration. Dehydrohalogenation of the phosphonium salts **23** with excess starting ylide provides a C-substituted ylide (*transylidation reaction*) (Eq. 2.36).

$$Ph_3P{=}CHR \xrightarrow{R'X} \underset{\mathbf{23}}{[Ph_3PCH_2R]^+X^-} \xrightarrow{Ph_3P=CHR} Ph_3P{=}CRR' \qquad (2.36)$$

The transylidation reaction proceeds the most easily, when the α carbon atom is connected to an electron-accepting group R which increases the CH-acidity of the phosphonium salt **23**. The starting ylide then readily dehydrochlorinates the phosphonium salt to form a new, less basic ylide.

2.2.2.1 Acylation

Acylation of phosphorus ylides is a widely used reaction for constructing carbon frameworks previously only obtained with difficulty. The acylation of phosphorus ylides is a accessible method for the preparation of carbonyl stabilized ylides. Numerous examples have been described of acylation of phosphorus ylides with carboxylic acid derivatives (esters, anhydrides, chlorides),[68,76,119–127] with chloroformate,[123] and with acylimidazoles.[128]

a) Acid Halides

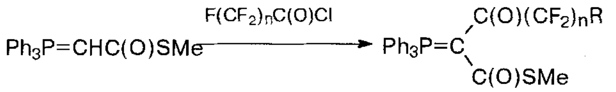
Reactions of phosphonium ylides with acid chlorides usually result in nucleophilic replacement of the acyl chloride with a ylide carbanion to produce a phosphonium salt.

The phosphonium salt cannot be usually isolated because it is more acidic than the starting ylide and gives up a proton to form a new C-acylated ylide and a phosphonium salt (Eq. 2.37).[125]

The general scheme of acylation includes the reaction of 2 equiv. ylide with 1 equiv. acyl halide. A typical example of the acylation of phosphorus ylides is the reaction of methylthiocarbonylmethylide with perfluoroacyl chlorides (Eq. 2.38):[76]

$$Ph_3P{=}CHR \xrightarrow{R'C(O)Cl} [Ph_3\overset{+}{P}CHRC(O)R']\ Cl^- \xrightarrow[{[Ph_3P^+CH_2R]Cl^-}]{Ph_3P=CHR} Ph_3P{=}CRC(O)R' \qquad (2.37)$$

24



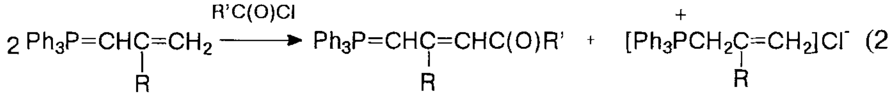
(2.38)

R=Cl, F; n=2,3,5,7

Triphenylphosphonium pentafluoropropionylcarbomethylthio methylide (Eq. 2.38)[76]

Pentafluoropropionyl chloride (3.3 g, 0.018 mol) was slowly added with stirring to a suspension of triphenylphosphonium carbomethylthiomethylylide (9.5 g, 0.027 mol) in absolute benzene (300 mL) in a flask with a dry ice–ethanol cooled condenser. After stirring of the reaction mixture at room temperature for 4 h at +20°C and standing overnight, the precipitate was removed by filtration and washed with absolute benzene. Evaporation of the combined benzene solution gave a solid which was recrystallized from methanol to give desired product. Yield 6.5 g (97%), mp 129–130°C.

Acylation of allylphosphonium ylides with acyl and formyl chlorides proceeds at the γ-carbon atom with the formation of the corresponding ylides (Table 2.2, Eq. 2.39) [129,130].

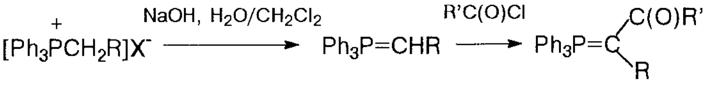


$$2\,Ph_3P{=}CH\underset{R}{C}{=}CH_2 \xrightarrow{R'C(O)Cl} Ph_3P{=}CH\underset{R}{C}{=}CHC(O)R' + [Ph_3\overset{+}{P}CH_2\underset{R}{C}{=}CH_2]Cl^- \qquad (2.39)$$

R=H, Me, OMe; R'=Me, CH=CHCO2Me

This scheme of acylation requires twofold excess of the starting ylide; usually a cheap and accessible compound. Nevertheless because of transylidation, different methodologies have been proposed to avoid the loss of one equivalent of starting ylide. Thus employment of bases stronger than the starting ylide enables the acylation to be performed with an equimolecular ratio of starting reagents. Use of biphasic systems results in the ready acylation not only of stabilized ylides, but also of semi-stabilized ylides. Although arylmethylides are sensitive to hydrolysis, the reaction provides C-substituted ylides in high yields because of the high rate of acylation. Benzylides are formed in the organic phase when solutions of benzyl-triphenylphosphonium halides are stirred with 50% aqueous alkali, because of the action of OH$^-$ ions transported into organic medium by the phosphonium cation; the use of special phase-transfer catalysts is thus unnecessary.

The addition of the acid chloride to this solution leads to the formation of acylated ylide.[124] This methodology considerably simplifies the synthesis of keto-ylides. Listvan and coworkers acylated arylylides with carboxylic acid chlorides in biphasic systems and obtained triphenylphosphonium aryl(acyl)methylides (Eq. 2.40):[68,126]



$$[Ph_3\overset{+}{P}CH_2R]X^- \xrightarrow{NaOH,\ H_2O/CH_2Cl_2} Ph_3P{=}CHR \xrightarrow{R'C(O)Cl} Ph_3P{=}C\genfrac{}{}{0pt}{}{C(O)R'}{R} \qquad (2.40)$$

25

Table 2.2. Acylation of phosphonium ylides (Eq. 2.37)

R	R'	Yield of **24**, %	mp	Ref.
H	Me	51	200-202 °C	119
H	CH_2Ph	-	147-148	119
H	CH_2CH_2Ph	49	148-150	119
H	Ph	71	178-180	119
H	$4\text{-}O_2NC_6H_5$	93	176-178	119
Me	CH=CHPh	73	205-208	119
Me	Ph	71	170-172	119
Pr	CH_2CH_2Ph	30	147-149	119
Ph	Me	73	68	119
Ph	Ph	63	58	119
CO_2Me	Ph	83	133-135	119
COSMe	C_2F_5	97	129-130	76
COSMe	C_3F_7	90	135-136	76
COSMe	C_7F_{15}	80	100-110	76
COSMe	$Cl(CF_2)_3$	90	151-152	76
CO_2Me	CH_2Cl	91	132	121
CO_2Et	CH_2Cl	90	136	121
CN	CH_2Cl	90	185-186	121
CN	CH_2Br	90	164	121
CO_2Me	CCl_3	83	144-146	121
H	CO_2Me	80	164	120
Pr	COMe	96	105	120
Ph	COMe	80	155	120

General method of preparation of triphenylphosphonium aryl(acyl) methylides in biphasic systems (Eq. 2.40, Table 2.3)[68,126]

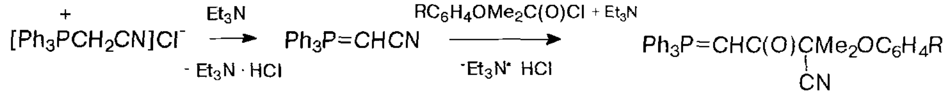
A solution of cyanomethyltriphenylphosphonium chloride (0.01 mol) was dissolved in dichloromethane (30 mL) and added dropwise with stirring to 5–10 mL aqueous sodium hydroxide (50%). The reaction mixture was stirred for 10–15 min and a solution of ethyl chloroformate (0.01 mol) in dichloromethane (10 mL) was added. The mixture was stirred for 10 min and then diluted with water. The organic layer was separated, the solvent was evaporated, and the residue was crystallized from ethanol–water, 3:1, to give a colorless solid. Yield 60%, mp 205°C.

Triphenylphosphonium 3-fluorophenyl(benzoyl)methylide (Eq. 2.40; Ar = 3-FC_6H_4, R = Ph) A solution of 3-fluorobenzenetriphenylphosphonium bromide (2.26 g) in dichloromethane (30 mL) was mixed with an aqueous solution of NaOH (50%, 5 mL) and a solution of benzoyl chloride (0.7 g) in dichloromethane (5 mL) was added dropwise. The reaction mixture was stirred for 5 min and was then diluted with water. The organic layer was separated, the solvent was evaporated, and the residue was crystallized from aqueous alcohol. The desired product was dried at 110°C. Yield 52%, mp 195–196°C

Table 2.3. Acylation of phosphorus ylides with carboxylic acid chlorides under biphasic conditions (Eq. 2.40)

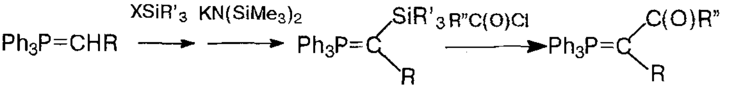
R	R'	Yield of **25**, (%)	mp	Ref.
Ph	Ph	62	193° C	126
$C_{10}H_{17}$	Ph	70	205	126
$C_{10}H_{17}$	C_2H_5O	35	199	126
Ph	4-$O_2NC_6H_4$	48	230-231	124
3-FC_6H_4	Ph	52	195-196	124
2-$C_{10}H_6$	Ph	65	210-211	124
4-Me-1-$C_{10}H_6$	4-$O_2NC_6H_4$	45	208	124
4-PhC_6H_4	3-$O_2NC_6H_4$	50	210	126
4-$O_2NC_6H_4$	3-$O_2NC_6H_4$	65	190	126
4-$PhC(O)C_6H_4$	Ph	80	197	126

Trippett performed the acylation of phosphorus ylides in the presence of triethylamine.[133] The deprotonation of triphenylcyanomethylphosphonium chloride with triethylamine and subsequent reaction with acyl chloride in the presence of the triethylamine results in C-acylylides in 81–94% yield (Eq. 2.41):[54]



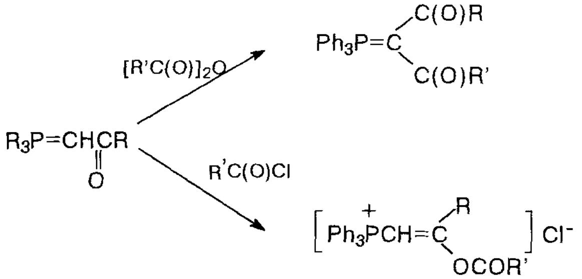
$$[Ph_3\overset{+}{P}CH_2CN]Cl^- \xrightarrow[-\,Et_3N\cdot HCl]{Et_3N} Ph_3P{=}CHCN \xrightarrow[\cdot Et_3N^{+}\,HCl]{RC_6H_4OMe_2C(O)Cl\ +\ Et_3N} Ph_3P{=}CHC(O)\underset{CN}{C}Me_2OC_6H_4R \qquad (2.41)$$

Yadav et al developed the acylation of stabilized P-ylides at α–carbon by acyl chlorides in the presence of activated zink dust.[128c] Bestmann has reported that silylated alkylylides react with a variety of acylating agents to give β–ketoylides in good to excellent yields (Eq. 2.42)[54]:



(2.42)

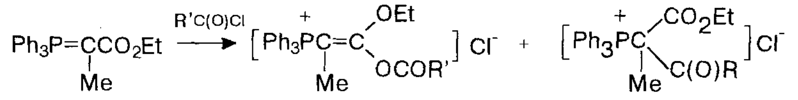
Acylation of β–ketoylides probably initially first furnishes the products of addition of acyl chloride to the oxygen atom of the carbonyl group. Then O-acylated phosphonium salts rearrange into C-acylated phosphonium salts, dehydrochlorination of which provides C-acylated ylides. The acylation of β–ketoylides with carboxylic acid anhydrides provides C-acylated phosphorus ylides. In contrast to the behavior of anhydrides, acetyl chloride furnishes the O-acylated phosphonium salt. The isomerization of the O-acylated compound into the C-acylated ylide was effected in the presence of tetrabutylammonium acetate in chloroform. Hence the O-acylated product is formed under conditions of kinetic control, whereas the C-acylated product is, unquestionably, thermodynamically more stable (Scheme 2.7): [173]



R=Alk, Ph; R'=Alk, Ph

Scheme 2.7

Abel and coworkers showed by low-temperature ^1H, ^{13}C, and ^{31}P NMR spectroscopy that the reaction of triphenylphosphonium carboethoxyethylide with acyl chlorides yields the O-acylated phosphonium salts, stable below 0°C, which at room temperature rearrange smoothly to the corresponding C-acylated phosphonium salts (Eq. 2.43)[131]:



$$Ph_3P=\underset{Me}{C}CO_2Et \xrightarrow{R'C(O)Cl} \left[Ph_3\overset{+}{P}\underset{Me}{C}=C\begin{matrix}OEt\\OCOR'\end{matrix}\right]Cl^- + \left[Ph_3\overset{+}{P}\underset{Me}{C}\begin{matrix}CO_2Et\\C(O)R\end{matrix}\right]Cl^- \tag{2.43}$$

R=Me, $CH_2CH_2CO_2Me$, $CH_2CH_2CO_2CH_2Ph$

Triphenylphosphonium methylide reacts with imidoyl chlorides to afford ylides **26** containing a C=N group on the ylidic carbon atom[132]; these were used for the synthesis of α,β-unsaturated ketimines (Eq. 2.45):

$$Ph_3P=CH_2+RN=C(R')Cl \longrightarrow \underset{\mathbf{26}}{Ph_3P=CHC(R')=NR} \xrightarrow{R''CHO} R''CH=CHC(R')=NR' \tag{2.44}$$

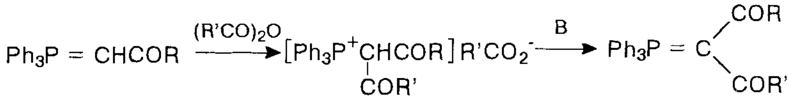
R=Ph, C_6H_4Me; R'=Ph, OMe, SMe

General method of the preparation of ylides ***26*** (Eq. 2.45)[132]

A suspension of methyltriphenylphosphonium bromide (5.0 g, 14 mmol) and sodium amide (1.5 g) in dry benzene (50 mL) was stirred for 12 h in a stoppered flask at room temperature. Then the precipitate was separated and the ammonia was removed in vacuo. A solution of imidoyl chloride (6 mmol) in benzene (10 mL) was added to the solution. The mixture was left to stand for 1 h at room temperature and the phosphonium salt was separated. The mother solution was treated with charcoal and then evaporated under vacuum The residue was crystallized from chloroform–petroleum ether. Yield 63–77%.

b) Acid Anhydrides

Acid anhydrides are effective acylating agents for phosphonium ylides. The reaction of triphenylphosphonium carboalkoxymethylides with linear acid anhydrides furnishes the phosphonium salts. Treatment of the salts with aqueous sodium hydroxide or triethylamine affords the acylated ylide **27** (Eq. 2.46, Table 2.4)[122].



$$Ph_3P=CHCOR \xrightarrow{(R'CO)_2O} [Ph_3P^+\underset{COR'}{CHCOR}]R'CO_2^- \xrightarrow{B} Ph_3P=C\begin{smallmatrix}COR\\COR'\end{smallmatrix} \qquad (2.45)$$

B=NaOH, Et_3N

27

Table 2.4. Acylation of phosphorus ylides with acid anhydrides (Eq. 2.45)[122]

A	R	Yield of **27**, (%)	mp
Me	Me	83	167-169°C
Me	Ph	97	172-173
Ph	Ph	89	191-192
Me	4-$O_2NC_6H_4$	42	190-191
OEt	Me	75	172-174
OEt	Et	50	123-125
OEt	Pr	54	132-133
OEt	Cl_3C	54	161-162
OMe	$ClCH_2$	24	138-139

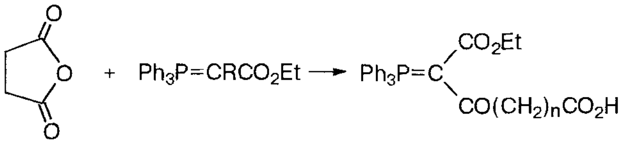
Acylation of triphenylphosphonium carboethoxymethylide with acetic anhydrides (Eq. 2.45)[122]

A 1:1 mixture of triphenylphosphonium carbethoxymethylide and acetic anhydride was heated without solvent at 100–120°C for 2 h. Treating the cold reaction mixture with ethyl acetate gave the intermediate phosphonium salt (yield 75%, mp 99°C). This was converted into the ylide in almost quantitative yield by treatment with aqueous sodium carbonate or by heating at 140°C and 0.01 mmHg for 0.5 h. Crystallization of the ylide from ethyl acetate gives a product with mp 172–174°C.

Preparation of triphenylphosphonium N,N-diethylamidocarbonyl(trifluoracetyl) methylide

N,N-diethylamidocarbonyl(trifluoracetyl)methyltriphenylphosphonium bromide (1.82 g, 4 mmol) in anhydrous THF (20 mL) was cooled in an ice–water bath under nitrogen and treated with triethylamine (0.81 g, 8 mmol) with stirring. The mixture was stirred for 15 min and treated with trifluoroacetyl anhydride (0.86 g, 4.1 mmol) dropwise and left to stand for 1 h. The mixture was poured into water and filtered. The precipitate was purified by recrystallization from methanol to give the ylide. Yield 1.64 g (87%), mp 198–200°C

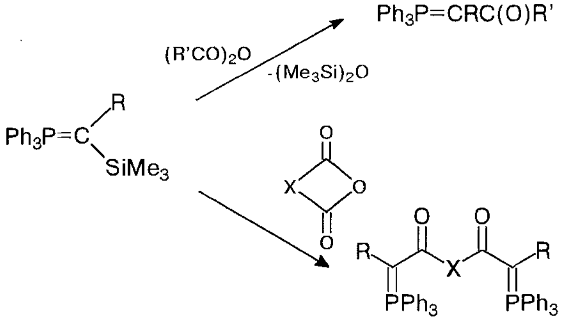
Cyclic anhydrides react differently with phosphonium ylides. Glutaric anhydride reacts analogously with linear anhydrides undergoing ring opening to a phosphonium carboxylate.[122d] Phthalic anhydride, however, reacts with the same ylides to afford the product of Wittig reaction on the carbonyl group, an enolate lactone. A similar result was obtained with succinic and maleic anhydrides (Eq. 2.46) . [122c]



(2.46)

Anhydrides of acyclic carboxylic acids acylate phosphorus ylides smoothly, whereas reaction of C_4 and C_5 cyclic carboxylic acid anhydrides with ylides leads to the formation of enol lactones.

The reaction of the triphenylphosphonium bis(trimethylsilyl)methylide with carboxylic acid anhydrides in 1:1 ratio proceeds to give keto-ylides in very good yields. The reaction of silylated ylides with anhydrides of cyclic carboxylic ylides provides bis-ylides which are the starting compounds for a number of interesting transformations (Scheme 2.8).[54,55]



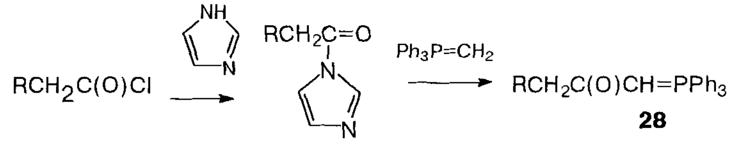
Scheme 2.8

If reaction of the acylating reagent with the ylide gives a phosphonium-salt-bearing anion which is a sufficiently strong base to deprotonate the acylated phosphonium salts, then the reaction proceeds in a 1:1 reagent ratio. Thus, reaction of acylimidazoles with phosphorus ylides proceeds with an equimolecular ratio of reagents and results in the formation of acylylides in good yields.[128a,b] Acylimidazoles can be obtained from an acyl chloride and an imidazole by a one-pot method (Table 2.5, Eq. 2.47).

The authors warn that for generation of a triphenylphosphonium methylide from a phosphonium salt by this reaction it is necessary to use phenyllithium, because butyllithium replaces phenyl groups on the phosphorus with butyl groups

General method for the acylation of ylides with acylimidazole (Eq. 2.47, Table 2.5)[128b]

An ethereal solution of acyl chloride (1 mol) was added slowly, over 15 min, at 5°C, under nitrogen to a stirred solution of imidazole (0.2 mol) in THF–Et_2O (1:1, 250 mL). After addition the reaction mixture was stirred for 30 min. The resulting precipitate of imidazole chloride was removed by filtration under a nitrogen and washed with ether. A slurry of methyltriphenylphosphonium bromide (0.1 mol) in ether (1000 mL) was treated with phenyllithium (0.1 mol) in ether–benzene at 25°C for 1.5 h. An ethereal solution of imidazole was then added to the ylide at –70°C over a period of 30 min. The reaction mixture was left to warm to +25°C and poured into dilute hydrochloric acid (2000 mL) and shaken with ether (1000 mL). The aqueous phase containing a heavy oil was separated. The insoluble phase is imidazole hydrochloride. The aqueous phase was made alkaline (pH 10) with potassium carbonate and the oil which separated was extracted with benzene or toluene. The organic extract was washed with an aqueous solution of sodium carbonate (2%), then with an aqueous solution of sodium chloride (1%), dried with sodium sulfate and evaporated under vacuum. The residue was recrystallized from hexane or ether–hexane. *Yields of desired products **28** are 50–60%.*



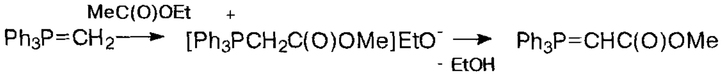
(2.47)

Table 2.5. Acylation of phosphorus ylides with acylimidazole (Eq. 2.47) [128a,b].

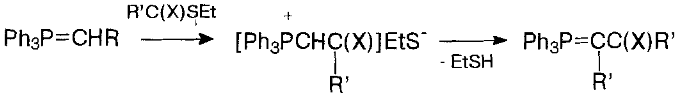
R	Yield of **28**, (%)	mp
Bu(Me)CH	55	83-85° C
c-$C_6H_{11}CH_2CH_2$	56	83-84
c-$C_6H_{11}CH_2$	53	133-135
C_7H_{15}	52	81-83
$MeOCH_2CH_2CH_2$	31	75-78
1-Methyladamantan	45	224-225

c) Esters

Wittig found that phosphorus ylides react with ethyl benzoate to produce triphenylphosphonium phenacylides. The reaction of non-stabilized phosphorus ylides with esters or thioethers of carboxylic acids furnishes C-acylated phosphorus ylides in high yields. Ethylate or mercaptide anions deprotonate the intermediate to form the C-acylated ylide (Eq. 2.48; 2.49)[31,133,134]:



$$Ph_3P{=}CH_2 \xrightarrow{MeC(O)OEt} [Ph_3\overset{+}{P}CH_2C(O)OMe]EtO^- \xrightarrow[-\,EtOH]{} Ph_3P{=}CHC(O)OMe \qquad (2.48)$$



$$Ph_3P{=}CHR \xrightarrow{R'C(X)SEt} [Ph_3\overset{+}{P}\underset{R'}{\underset{|}{C}}HC(X)]EtS^- \xrightarrow[-\,EtSH]{} Ph_3P{=}\underset{R'}{\underset{|}{C}}C(X)R' \qquad (2.49)$$

Depending on the presence of lithium salts the reaction follows one of two pathways. In both reactions initial attack of the ylide carbanion on the ester carbonyl group affords an intermediate betaine which might be complexed or free. If the lithium salt is absent and the betaine is uncomplexed it is free to transfer oxygen to phosphorus in a

Wittig reaction, affording an enol ether as product. If the oxygen is complexed, particularly with lithium, such transfer is slowed and ejection of alkoxide becomes the predominant route. Alkoxide or other bases in the solution remove the acidic proton from the α carbon to phosphorus, forming a new acylated ylide. Cristau obtained triphenylphosphonium phenacylide in 96% yield by reacting the ylide-carbanion with ethyl benzoate[135].There is considerable preparative interest in the reaction of methylides with formic acid esters, leading to the formation of phosphorus ylides stabilized by an aldehyde group at the α carbon atom. These ylides are interesting, because they allow to increase a carboxylic chain on one atom of carbon to replace an aldehyde group on vinylaldehyde.[136] On the other hand, reaction of ethyl formate with a variety of substituted ylides (R = COOEt, CH=CHPh) afforded good yield of the enol ether (Eq. 2.50):[35,39]

$$[Ph_3PMe]Br^- \xrightarrow{BuLi} Ph_3P{=}CH_2 \xrightarrow{EtOCHO} Ph_3P{=}CHCHO \xrightarrow{RCHO} Ph_3P{=}CHCHO \qquad (2.50)$$

Preparation of triphenylphosphonium α-formylmethylide (Eq. 2.50)[137]
An ethereal solution of butyllithium (1.16 N; 25 mL) was added dropwise with stirring to a stirred suspension of methyltriphenylphosphonium bromide (10.7 g) in ether (100 mL). The solution was stirred for 0.5 h and then slowly added to a stirred solution of ethyl formate (2.7 g) in ether (50 mL). After 0.5 h the solution was extracted with dilute hydrochloric acid (2 x 100 mL). The combined extracts were treated with dilute sodium hydroxide and extracted with benzene (3 x 200 mL). The solvent was evaporated and the residue crystallized from acetone. Yield 6.1 g, mp 186–187°C (dec.)

The improved method has been proposed for the preparation of α-formylalkylides. It consists in the addition of potassium *tert*-butoxide, and then the ethyl formate to the phosphorus ylide (Eq. 2.51)[138]:

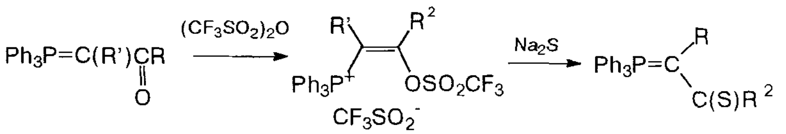
$$\underset{R=H,\ Me}{[Ph_3PCH_2R]Br^-} \xrightarrow{BuLi} Ph_3P{=}CHR \xrightarrow{t\text{-}BuOK/\ EtOCHO} Ph_3P{=}C(R)CHO \qquad (2.51)$$

Triphenylphosphonium α-formylethylide (Eq. 2.51)[138]
Butyllithium in hexane (1.1 equiv.) was added dropwise to a mechanically stirred suspension of ethyltriphenylphosphonium iodide (0.01 mol) in tetrahydrofuran (33 mL) at approx. 22°C under a nitrogen atmosphere. The resulting red solution was stirred for 1 h, then cooled to 0°C. Freshly sublimed potassium *tert*-butoxide (1.1 equiv.) was added followed by rapid addition of ethyl formate (2.5 equiv., neat, dried over P_2O_5). The reaction mixture was kept at 0°C for 15 min and then quenched with hydrochloric acid (1 M, 12.5 mL). After addition of dichloromethane (75 mL) and 10% aqueous alkali until the pH of the aqueous layer was 8 the reaction mixture was stirred for 30 min. The aqueous layer was separated and further extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried with magnesium sulfate and evaporated under vacuum. The residue was recrystallized from dichloromethane–ether to afford a white solid, mp 180–182°C in 84% yield. Recrystallization from benzene–hexane afforded the product, mp 213–217°C.

The reaction of phosphonium ylides with thiol esters is an effective means of improving the efficiency of the acylating reaction because the thiolate anion produced in the first step is sufficiently basic to convert the initially formed salt to its ylide thereby avoiding the consumption of one half of the starting ylide in a transylidation reaction (Eq. 2.52).

$$Ph_3P{=}CHR \xrightarrow{R'C(O)SEt} [Ph_3P^+CHRC(O)R']EtS^- \xrightarrow[-EtSH]{} Ph_3P{=}CRC(O)R' \tag{2.52}$$

Li and Xian used tellurester for acylation of acylylides.[139] Bestmann developed interesting method for conversion of ketoylides to thioketoylides by reaction of the corresponding acyl ylides with trifluoromethansulfonic anhydrides followed by treatment with sodium sulfide (Eq. 2.53)[140]. The reaction of unstabilized phosphonium ylides with ethyl nitrate leads to the formation of 1-nitroalkylides, which were isolated in good yields as crystalline compounds (Eq. 2.54):[141]

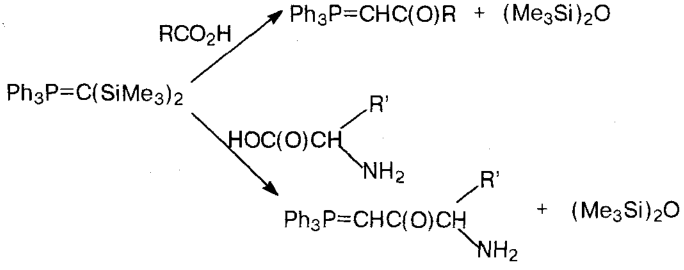


(2.53)

$$2Ph_3P{=}CHMe + EtONO_2 \longrightarrow Ph_3P{=}C(Me)NO_2 + [Ph_3P^+Et]EtO \tag{2.54}$$

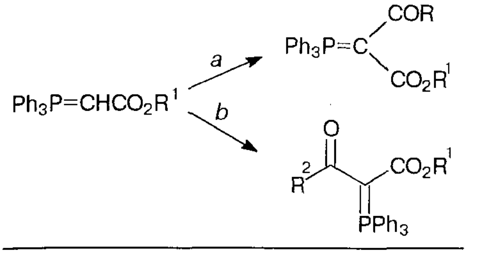
d) Reaction with Carboxylic Acids

Triphenylphosphonium bis(trimethylsilyl)methylide reacts with carboxylic acids to give keto-ylides. This method has several advantages over alternatives for the preparation of simple β-ketoylides and provides the first synthesis of α-aminoacylylides (Scheme 2.9):[54,142,143]



Scheme 2.9

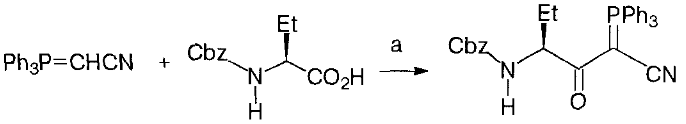
Methods specifically for the acylation of stabilized phosphorus ylides have also been reported. The first involves reaction with acyl anhydrides or acyl chlorides in the presence of bis(trimethylsilyl)acetamide, while the second couples the ylides with carboxylic acids in the presence of *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide to furnish new diacylated phosphorus ylides (Scheme 2.10)[144,145]:



a = R^2COX, $CH_3CON(SiMe_3)_2$, *b*-R^2CO_2H, $Me_2N(CH_2)_3N{=}C{=}NEt$

Scheme 2.10

Both methods are substantially superior to earlier approaches[144,145]. This reaction enables the introduction of amino acids into the structure of stabilized P-ylides (Eq. 2.55):

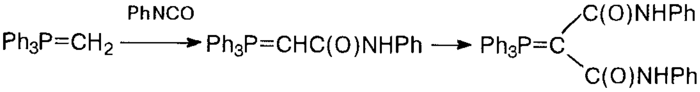


(2.55)

a -R^2COX, $CH_3CON(SiMe_3)_2$

e) Heterocumulenes

Phosphorus ylides containing one or two hydrogen atom on the α-carbon atom are easily acylated with isocyanates to furnish mono- or diacylated ylides (Eq. 2.56)[143,146,147]:

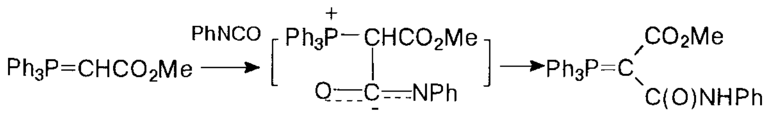


$$Ph_3P{=}CH_2 \xrightarrow{PhNCO} Ph_3P{=}CHC(O)NHPh \longrightarrow Ph_3P{=}C\begin{matrix} C(O)NHPh \\ C(O)NHPh \end{matrix} \qquad (56)$$

Triphenylphosphonium di(phenylcarbamoyl)methylide[143]

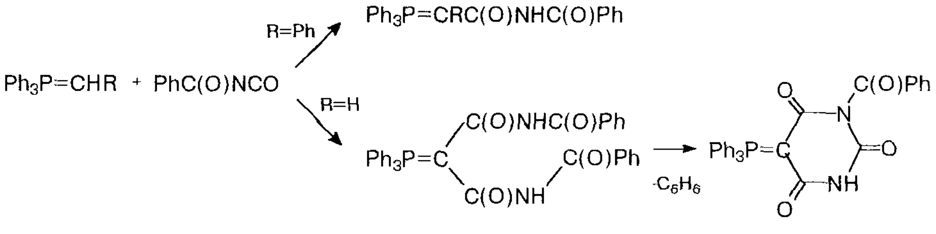
A solution of butyllithium (1.4 N, 8 mL) in ether was added dropwise under nitrogen to a stirred suspension of methyltriphenylphosphonium bromide (3.7 g) in ether (30 mL). A solution of phenylisocyanate (2.58 g) in ether (10 mL) was then added. The reaction mixture was stirred for 0.5 h and the ether was removed under reduced pressure. The residue was crystallized from aqueous ethanol. After recrystallization from *n*-butanol the triphenylphosphonium di(phenylcarbamoyl)methylide was obtained with mp 172–173°C

The reaction proceeds via the formation of intermediate betaines, which rearrange into more stable phosphonium ylides (Eq. 2.57):



$$Ph_3P{=}CHCO_2Me \xrightarrow{PhNCO} \left[\begin{matrix} Ph_3\overset{+}{P}-CHCO_2Me \\ | \qquad | \\ \overset{-}{O}{=}C{=}NPh \end{matrix}\right] \longrightarrow Ph_3P{=}C\begin{matrix} CO_2Me \\ C(O)NHPh \end{matrix} \qquad (2.57)$$

The reaction of C-substituted ylides with acylisocyanate affords acyclic C-acylated ylide in high yield, whereas the triphenylphosphonium methylide furnishes a cyclic ylide (Scheme 2.11).



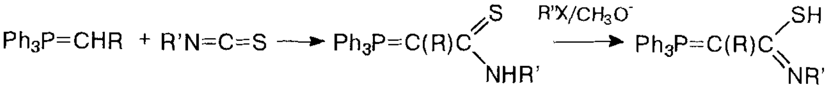
Scheme 2.11

The reaction between benzoylisocyanate and an ylide, containing a hydrogen atom on the ylide carbon gives a betaine in the initial step. This betaine then undergoes intramolecular cyclization with elimination of benzene[147]: The reaction of phosphorus ylides with alkyl-, aryl-, and acylisothiocyanates furnishes triphenylphosphonium amidothio-carbonylalkylides in high yield (Eq. 2.58)[148–150]:

$$Ph_3P{=}CHR^1 \xrightarrow{R^2N{=}C{=}S} Ph_3P{=}CR^1C(S)NHR \tag{2.58}$$

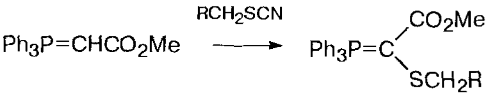
R^1=H, Me, Ph, CO_2Me, C(O)Alk, C(O)Ar; R^2=Me, Ph, C(O)Ph

Amidothiocarbonylalkylides are starting compounds for the preparation of various organic compounds, including new phosphorus ylides (Eq. 2.59)[151]:



$$Ph_3P{=}CHR + R'N{=}C{=}S \longrightarrow Ph_3P{=}C(R)C\begin{matrix}{=}S\\ NHR'\end{matrix} \xrightarrow{R'X/CH_3O^-} Ph_3P{=}C(R)C\begin{matrix}SH\\ {=}NR'\end{matrix} \tag{2.59}$$

Stabilized phosphorus ylides react with fluoroalkylthiocyanates to furnish new ylides containing a thiofluoroalkyl group on the α carbon atom (Eq. 2.60). This method enables the introduction of a perfluoroalkyl chain into the structure of a stabilized phosphonium ylide[152].



$$Ph_3P{=}CHCO_2Me \xrightarrow{RCH_2SCN} Ph_3P{=}C\begin{matrix}CO_2Me\\ SCH_2R\end{matrix} \tag{2.60}$$

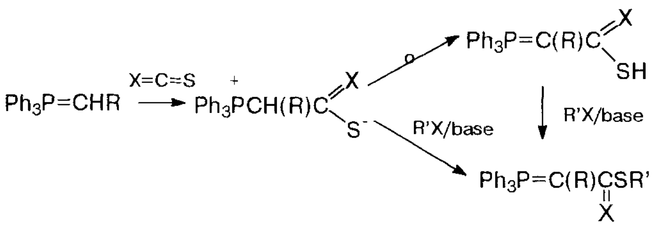
R=Ph, C_3H_7, R_FCH_2

Pandolfo and coworkers studied the reaction of the carbon suboxide with stabilized phosphorus ylides bearing a hydrogen atom on the ylidic carbon atom. The reaction has been investigated and shown to give the bis-ylide (Eq. 2.61)[150]:

$$Ph_3P{=}CHCN + O{=}C{=}C{=}C{=}O \longrightarrow Ph_3P{=}C(CN)COCH_2COC(CN){=}PPh_3 \qquad (2.61)$$

Reaction of carbon suboxide with triphenylphosphonium cyanomethylide (Eq. 2.63)[150] Triphenylphosphonium cyanomethylide (0.55 g, 1.82 mmol) was dissolved in toluene–dichloromethane (5:1, 50 mL) and a solution of carbon suboxide (0.91 mmol) in toluene was added at room temperature with stirring to give a light yellow reaction mixture. The solution was concentrated under vacuum to 40 mL and the solid was removed by filtration, washed with toluene and dried under vacuum. Yield 0.450 g (73%), mp 243–244°C.

Phosphorus ylides react with carbon disulfide and COS with the formation of a betaine which can be alkylated alkyl halides (Scheme 2.12, Table 2.6)[153,154]:



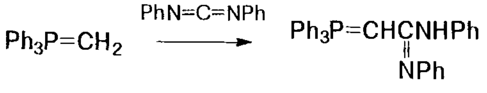
29

Scheme 2.12

Table 2.6. Reaction of phosphorus ylides with carbon disulfide and COS (Scheme 2.12)

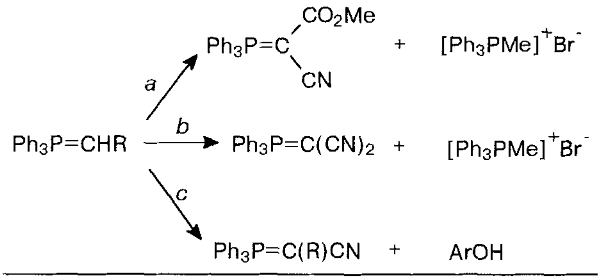
R	R'	X	Yield of **29**, (%)	Ref.
H	Me	O	86	153
Me	Et	O	77	153
Ph	Me	O	69	153
H	Et	S	93	154
Me	Et	S	96	154
Me	Bz	S	89	154
Ph	Me	S	94	154

Triphenylphosphonium methylide reacts with diphenylcarbodiimide to produce an ylide containing an amidine group on the ylidic carbon atom (Eq. 2.62)[155–157]:



$$Ph_3P{=}CH_2 \xrightarrow{PhN{=}C{=}NPh} Ph_3P{=}CH\underset{\underset{NPh}{\|}}{C}NHPh \qquad (62)$$

Triphenylphosphonium alkylides react with arylcyanates to provide P-ylides containing cyano groups on the α-carbon atom[157,158]. Triphenylphosphonium methylide react with arylcyanates to afford, depending on the ratio of reagents, phosphorus ylides bearing one or two cyano groups on the ylidic carbon atom (Scheme 2.13)[158,159].



a - BrCN, R=CO_2Me; b - BrCN, R=H;
c - ArOCN, Ar =4-$MeOC_6H_4$ R=H, Me, Pr, C_5H_{11}, Ph, CO_2Me

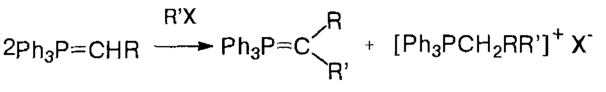
Scheme 2.13

Triphenylphosphonium methoxycarbonyl(cyan)methylide (Scheme 2.13).[158]
A solution of triphenylphosphonium methoxycarbonylmethylide (3.34 g, 0.01 mol) in benzene (15 mL) was placed in a flask and a solution of cyanogen bromide (0.529 g, 0.005 mole) in dry ether (5 mL) was added with stirring. The reaction mixture was left for 24 h and treated with water (1000 mL). The solid was removed by filtration, dried, and crystallized from ethanol. Yield 1.29 g (72%), mp 217–218°C. Reaction of keto-ylides with cyanogen bromide leads to the formation of ylides bearing cyano group on the ylidic carbon atom[156–158].

2.2.2.2 Alkylation

Alkylation of phosphonium ylides, and acylation, are widely explored methods for modification of the carbon frameworks of phosphorus ylides.[159-176] The alkylation of phosphorus ylides involving the attachment of alkyl groups to the ylidic carbon atom enables modification of simple phosphorus ylides, prepared by the salt method to furnish new mono- and disubstituted ylides. The alkylation of phosphorus ylides is a very effective means for placing different alkyl groups on one of two carbon atoms of the C=C double bond. The reaction furnishes ylides and phosphonium salts, which are impossible to obtain by the salt method. In contrast with acylation, the alkylation of phosphorus ylides often furnishes C-alkylated phosphonium salts, which do not undergo the transylidation reaction with starting ylides (Eq. 2.63).[22,159,167]
However the transylidation takes place when phosphorus ylides react with alkyl halides containing electron-accepting groups. The reaction of triphenylphosphonium carbomethoxymethylide with such alkyl halides as benzyl bromide, allyl bromide, bromoacetic ester, bromoacetonitrile, etc., proceeds a 2:1 ratio of reactants, resulting in C-alkylated phosphorus ylides **30** and phosphonium salts (Eq. 2.64, Table 2.7)[160-164]

$$Ph_3P{=}CH_2 \xrightarrow{MeI} [Ph_3\overset{+}{P}CH_2Me]\ I^- \tag{2.63}$$



$$2Ph_3P{=}CHR \xrightarrow{R'X} Ph_3P{=}C(R)R' + [Ph_3PCH_2RR']^+\ X^- \tag{2.64}$$

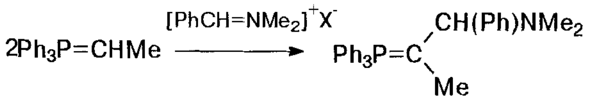
30

For example, the reaction of triphenylphosphonium methoxycarbonylmethylide (0.4 mol) with ethyl bromoacetate (0.2 mol) when heated under reflux in ethyl acetate for 2 h furnishes the phosphonium salt, in 95% yield, and the C-alkylated ylide, which after evaporation of the solvent and recrystallization of the residue from Et_2O was obtained in 98% yield (Table 2.7)

Table 2.7. Alkylation of phosphorus ylides (Eq. 2.64)

R	R'	mp	Yield of **30**,(%)	Ref
Ph	EtCOCH=CH	216-218° C	72	165
β-$C_{10}H_7$	4-$O_2NC_6H_4CH_2$	194-196	82	157
$PhCH_2$	i-PrCOCH=CH	185-188	36	165
CO_2Me	$PhCH_2$	186-187	75	160
CO_2Me	$CNCH_2$	138-139	89	160
CO_2Me	CH_2CO_2Me	157-158	98	160
CO_2Me	$CH_2CH=CH_2$	-	93	160
CO_2Me	$CH_2CH=CHPh$	-	81	160
CO_2Me	4-$O_2NC_6H_4CH_2$	154	88	157
CO_2Et	MeCOCH=CH	172-175	49	165
CO_2Et	i-PrCOCH=CH	138-140	90	165
C(O)Me	CH_2CO_2Me	148-150	74	163
C(O)Ph	CH_2CO_2Me	177-178	20	163
C(O)Ph	4-$O_2NC_6H_4CH_2$	181-185	82	157
C(O)Ph	4-$O_2NC_6H_4CH_2$	181-185	82	157
4-MeC_6H_4CO	4-$O_2NC_6H_4CH_2$	201-202	82	157
4-ClC_6H_4CO	4-$O_2NC_6H_4CH_2$	205	85	157
$C(O)CH_2CH_2Ph$	MeO_2CCH_2	130-131	40	163

C-Monosubstituted ylides undergo a transylidation reaction with α-chloroalkylamines to afford phosphonium 2-diaminoalkylides in good yields (Eq. 2.65)[161]:



$$2Ph_3P{=}CHMe \xrightarrow{[PhCH{=}NMe_2]^+X^-} Ph_3P{=}C(CH(Ph)NMe_2)(Me) \tag{2.65}$$

R=Ph, Bz, Me; X= Cl, CF_3SO_2O; R = Ph, Bz, Me; X = Cl, CF_3SO_2O

Alkylation of organometallic derivatives of phosphorus ylides proceeds with a 1:1 ratio of initial reagents. Thus, the treatment of the triphenylphosphonium cyanomethylide with sodium bis(trimethylsilyl)amide affords a highly reactive sodium derivative of the ylide which reacts easily with alkyl halides to form C-alkylated cyanylides (Eq. 2.66)[166a]:

$$Ph_3P{=}CHCN \xrightarrow{NaN(SiMe_3)_2} [Ph_3P{=}C{=}C{=}N]^-Na^+ \xrightarrow{RX} Ph_3P{=}C(R)CN \tag{2.66}$$

The alkylation enables the preparation of phosphorus ylides bearing vinyl or acetylenic groups on the ylidic carbon atom. Different examples of such reactions have been.

Thus, Zbiral reacted 2-chlorovinylketones with C-substituted phosphorus ylides, producing allylic ylides in good yields (Eq. 2.67).[65]. Bestmann reported the preparation of phosphorus ylides by reaction of alkynyl bromides with triphenylphosphonium methylide (Eq. 2.68)[166b]. Reaction of 1,1-dibromoolefins with triphenylphosphonium methylide proceeds with a 1:3 ratio of starting reagents to furnish triphenylphosphonium alkyneylides (Eq. 2.69)[166c]:

$$Ph_3P{=}CHR + R'C(O)CH{=}CHCl \rightarrow Ph_3P{=}C(R)CH{=}CHC(O)R' \qquad (2.67)$$

$$Ph_3P{=}CH_2 + RC{\equiv}CBr \rightarrow Ph_3P{=}CHC{\equiv}CR \qquad (2.68)$$

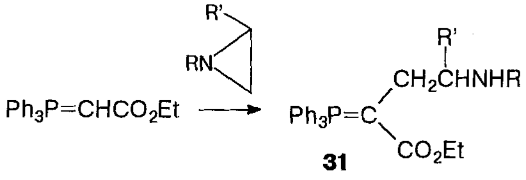
$$3Ph_3P{=}CH_2 + RCH{=}CBr_2 \rightarrow Ph_3P{=}CHC{\equiv}CR + 2[Ph_3P^+Me]Br^- \qquad (2.69)$$

Reaction of triphenylphosphonium methylide with dialkylaluminumalkylidenes in diethyl ether proceeds with replacement of the hydrogen atoms on the alkylidene group (Eq. 2.70). The reaction provides allylic ylides in 80% yield and dialkylaluminumamines, which were separated by crystallization from ether at –78°C. The reaction affords the *cis* form of the allylic ylides when R is *n*-alkyl and the *trans* form when R = *t*-Bu or Ph[168,169].

$$Ph_3P{=}CH_2 + [RCH_2CH{=}NAlBu\text{-}i_2]_2 \longrightarrow Ph_3P{=}CHCH{=}CHR + i\text{-}BuAlNH_2 \qquad (2.70)$$

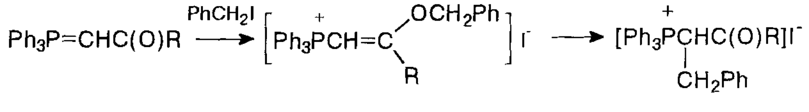
$R{=}n\text{-}Alk\ (C_1\text{-}C_8),\ t\text{-}Alk,\ Ph$

Heine described C-alkylation of triphenylphosphonium carboethoxymethylide with *N*-acyl and *N*-tosylaziridines (Eq. 2.71)[170]. The reaction proceeds when heated under reflux in toluene; aziridine ring opening affords new phosphonium 3-aminoalkylides **31** in excellent yields



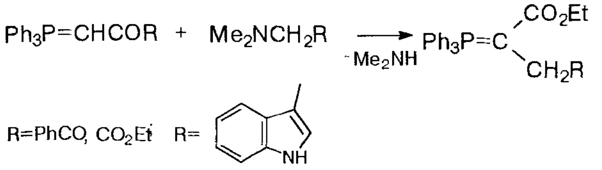
(2.71)

Alkylation of ketoylides with alkylhalides proceeds with the formation of O-acylated products. For example, the triphenylphosphonium phenacylmethylide is alkylated to form O-alkylated phosphonium salts, which then rearrange into C-alkylated phosphonium ylides (Eq. 2.72)[130,168,169,171-174]:



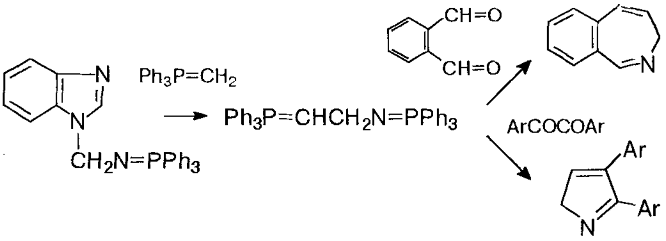
$$Ph_3P{=}CHC(O)R \xrightarrow{PhCH_2I} \left[Ph_3\overset{+}{P}CH{=}C\begin{matrix}OCH_2Ph\\R\end{matrix}\right]I^- \longrightarrow [Ph_3\overset{+}{P}\underset{\displaystyle CH_2Ph}{\underset{|}{C}}HC(O)R]I^- \qquad (72)$$

Mannich bases alkylate ketoylides when heated under reflux in toluene for 6–7 h (Eq. 2.73)[175]. For example, reaction of a mixture of triphenylphosphonium carboethoxymethylide (0.1 mol) and Mannich base (0.1 mol) under reflux in toluene (300 mL) for 6–7 h provides crystalline C-alkylated ylide in 72–92% yield:



(2.73)

1,2- and 1,3-Monoazabisylides have been prepared in situ by reaction of triphenylphosphonium methylide with iminophosphorane then treatment with butyllithium (Scheme 2.14). 1,3-Monoazabisylides are starting reagents for the preparation of isoquinoline, 2-azabutadiene, 2,3-diarylpyrroles, and 2-(3*H*)-benzasepine[176].



Scheme 2.14

So, alkylation is a useful method for modification of phosphorus ylides and construction of carbon frameworks, which provides a variety of new ylides for subsequent use in organic synthesis

2.2.2.3 Arylation

The reaction of phosphorus ylides with aromatic compounds containing activated halogen furnishes P-ylides containing aromatic substituents on the ylidic carbon atom. Thus, Papas and Ganchev showed, that reaction of stabilized ylides with picryl chloride and 2,4-dinitrobenzene furnishes C-aryl-substituted ylides (Eq. 2.74)[177]:

$$2Ph_3P{=}CHR + Ar\text{-}X \longrightarrow Ph_3P{=}C(R)Ar + [Ph_3PCH_2R]^+X^- \qquad (2.74)$$

$$Ar = 2,4,6\text{-}(O_2N)_2C_6H_2,\ 2,4(O_2N)_2C_6H_2$$

Triphenylphosphonium α–(2,4,6-trinitrophenyl) α–carbomethoxymethylide (Eq. 2.76) [177]

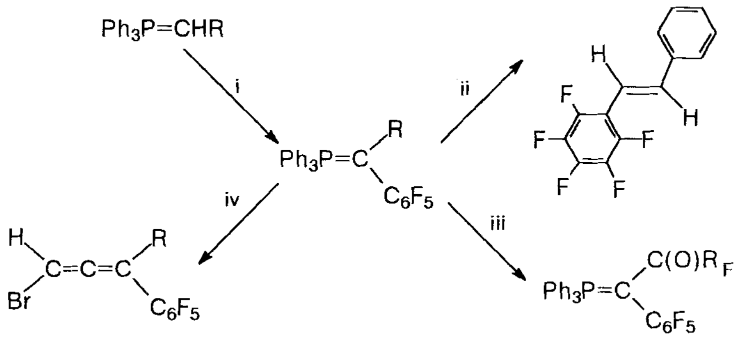
A mixture of triphenylphosphonium carboethoxymethylide (2.01 g, 0.006 mol) and picryl chloride (0.74 g, 0.003 mol) in benzene (20 mL) was heated on a steam bath for 1 h. The precipitate of phosphonium chloride was removed by filtration and washed with benzene. The filtrate was evaporated and the residue was recrystallized from methanol–water to yield 0.93 g (57%) of violet–red crystals of the desired ylide, mp 192–193°C.

Many examples have been reported of C–F bond cleavage in fluoroarenes by phosphonium ylides.[178–182] Pentafluorobenzenes C_6F_5X with electron-withdrawing substituents (NO_2 or CN) undergo CF bond cleavage at the 4-position under mild conditions (ether, room temperature) to give ylides the structure of which was verified by X-ray crystallography (Eq. 2.75):[178,179]

$$2Ph_3P{=}CHR + C_6F_5X \longrightarrow Ph_3P{=}C(C_6F_4X\text{-}4)R + [Ph_3PCHR]^+F^- \qquad (2.75)$$

X=NO_2, CN; R=Ph, C_6H_4Me-4; R= CO_2Me, CO_2Et, $CONMe_2$,

Nesmeianov reacted ylides with hexafluorobenzene to synthesize triphenylphosphonium pentafluorophenylmethylides which were then used for the preparation of fluorinated stilbenes according to the Wittig reaction[180]. A new one-pot synthesis of fluorinated bromoallenes was achieved by reaction of triphenylphosphonium pentafluoro-phenylmethylide with bromoacetyl bromide[181]. Triphenylphosphonium methylide reacts with hexafluorobenzene in 2:1 ratio in ether at room temperature to form triphenylphosphonium pentafluorophenylmethylide and triphenylphosphonium fluoride: The pentafluorophenylmethylide formed, without separation from the reaction solution, was reacted with fluorides or anhydrides of perfluoroalkanecarbonic acid to furnish triphenylphosphonium perfluoroacylpentafluorophenylmethylides in yields of 51–83% (Scheme 2.15)[182]



i - C_6F_6; THF, -20 °C ii - PhCHO,[180] iii - $[R_FC(O)]_2O$;[182] iv - $BrCH_2C(O)Br$, THF, -60°C[181]

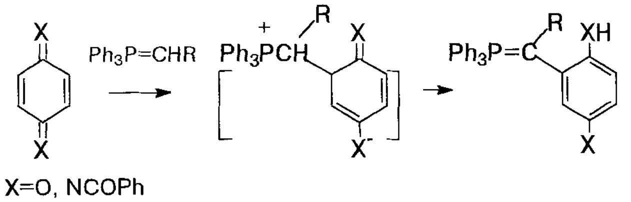
Scheme 2.15

α-Trifluoroacetylpentafluorophenylmethylide (Scheme 2.15)[182]

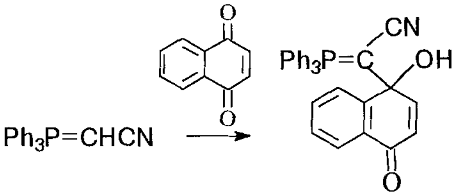
A solution of triphenylphosphonium methylide was prepared under nitrogen from methyltriphenylphosphonium bromide (6 g, 16.8 mmol) and phenyllithium (16.8 mmol) in absolute ether (80 mL). A solution of hexafluorobenzene (1.6 g, 8.6 mmol) in ether (8 mL) was added dropwise to this solution with stirring at –30°C. The stirred reaction mixture was then warmed to 25°C and left for 3 h at this temperature. The mixture was then cooled to

–78°C and a solution of trifluoroacetic acid anhydride (4.2 mmol) in ether (5 mL) was added. The mixture was left to warm to 25°C, stirred for 5 h at room temperature and left overnight. The precipitate was removed by filtration, the filtrate was evaporated, and the residue was chromatographed on a silica gel column with petroleum ether–ethyl acetate, 6:1, as eluent. Recrystallization from methanol gave the desired product in 83% yield, mp 209–210°C.

Phosphorus ylides react with quinones and quinone imines to afford C-arylsubstituted ylides (Eq. 2.76). The reaction probably proceeds via the formation of an intermediate betaine, which then rearranges into a new C-substituted ylide[183a-d]. Reaction of the triphenylphosphonium cyanomethylide with 1,4-naphthoquinone proceeds at the carbonyl group to give the new ylide-quinone adduct and the dimeric product (Eq. 2.77)[184]:



(2.76)



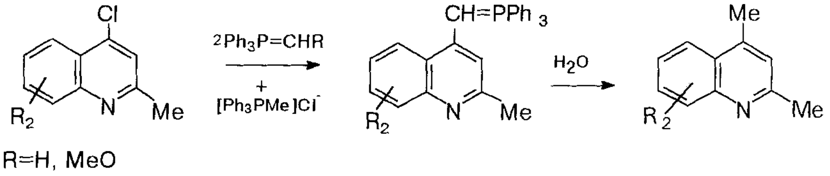
(2.77)

Taylor and coworkers[185,186] reacted phosphorus ylides with different aromatic compounds to obtain the appropriate ylides (Eq. 2.78; HetX = halides of pyridine, pyrazine, quinoline, isoquinoline, benzoxazole, 9-(tetrahydro-2-pyranyl) purine and others):

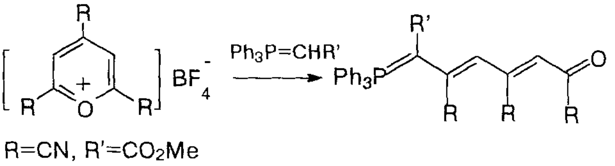
$$R_3P{=}CHR' + HetX \longrightarrow R_3P{=}C(R')Het + [R_3PCH_2(R')]^+X^- \qquad (2.78)$$

R= Bu, Ph: R'= H, Me,Et, Ph, Ar; X=Cl, Br, OSO_2Me

Reaction of active ylides with ring-substituted heterocyclic compounds leads to the formation of phosphorus ylides containing heterocyclic substituents on the ylidic carbanion. P-Ylides were hydrolyzed or introduced into the Wittig reaction to afford quinine and some quinine derivatives (Eq. 2.79)[187]. Pyrilium salts readily alkylate triphenylphosphonium methylide at the ylidic carbon atom with the formation of ylides which undergo the Wittig reaction with the formation of the aldehyde-trienes. The 2-*H*-pyransubstituted ylide was generated by the reaction of pyrilium tetrafluoroborate with triphenylphosphonium methylide (Eq. 2.80)[188]:



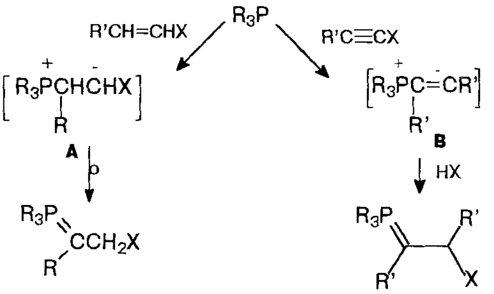
(2.79)



(2.80)

2.2.3 Addition of Tertiary Phosphines to Compounds Containing Multiple Bonds

Tertiary phosphines react by addition with a wide variety of compounds containing activated multiple bonds, providing phosphorus ylides which can be isolated in the pure state or used without isolation in a Wittig reaction. Detailed studies showed that addition of tertiary phosphine to a compound containing multiple bonds proceeds via the formation of betaine intermediates **A** and **B**. The betaine **A** undergoes a [1,2]-prototropic shift and is converted into a phosphorus ylide (Scheme 2.16). Intermediate **B** undergoes a different chemical transformation, for example, giving addition products of the ylide structure with proton-containing nucleophiles.



Scheme 2.16

2.2.3.1 Alkenes

Tertiary phosphines react with variety of conjugated alkenes to furnish interesting phosphorus ylides which can be used then as initial reactants in the Wittig reaction. If these ylides do not contain electron-withdrawing substituents *R* on the *a* carbon, they are reactive and can be introduced into the Wittig reaction with carbonyl compounds without isolation from the reaction mixture. Thus, the reaction of acrylonitrile and triphenylphosphine with benzaldehyde at 140°C affords a 23% yield of *trans*-4-phenyl-3-butenenitrile, with no mention made of the *cis*-isomer. It was proposed that the reaction was initiated by nucleophilic addition of triphenylphosphine to acrylonitrile to form an intermediate zwitterion A which underwent a prototropic shift to form an ylide (Eq. 2.81) which then reacted with a aldehyde in a Wittig reaction[167,168,190,191]:

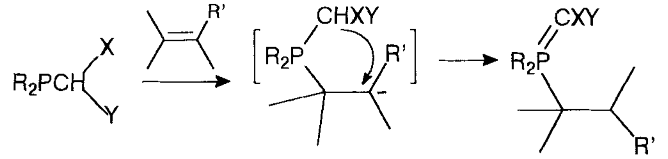
$$R_3P \xrightarrow{RCH=CH_2} \underset{\mathbf{A}}{[R_3\overset{+}{P}CH\overset{-}{C}H_2R']} \rightarrow R_3P=CHCH_2R' \qquad (2.81)$$

The reactions are of preparative interest, despite the low yields of the final products (30–40%), because of the accessibility of starting reagents. Bestmann and coworkers[191] by reflux of the mixtures of triphenylphosphine and ethyl acrylate with alkylaldehydes obtained olefins in 28–32%; these were then used as semiochemicals in the synthesis of insect pheromones (Eq. 2.82):

$$CH_2=CHCO_2Et \xrightarrow{Ph_3P\ +\ CH_3(CH_2)_nCHO} CH_3(CH_2)_n\underset{H}{C}=\underset{H}{C}CH_2CO_2Et \xrightarrow{LiAlH_4} CH_3(CH_2)_n\underset{H}{C}=\underset{H}{C}CH_2CH_2OH$$

$n = 3,7$ (2.82)

Trivalent phosphorus compounds containing an activated methylene group react readily with conjugated alkenes. The reaction is accompanied by prototropic shift from α carbon atom to the negatively charged β carbon atom in the zwitterionic intermediate (Eq. 2.83)[190]:



(2.83)

CXY =$C(CO_2Me)_2$,[190b] $CHSO_2CF_3$,[190b] $C(SO_2Ph)_2$,[190b] $CHCO_2Et$,[190b] CHPh,[175] R'=Ph, CO_2Et, CN, $CONH_2$,

The reaction of tertiary phosphines with α,β-non-saturated carbonyl compounds furnishes stabilized phosphorus ylides (Eq. 2.84). Thus *trans*-dibenzoylethylene add tertiary alkyl- and arylphosphines to form phenacyl(benzoyl) methylides, isolated in good yields as yellow crystalline substances (Eq. 2.85)[192,193]:

$$Ph_3P + RCH=CHC(O)R' \longrightarrow [Ph_3\overset{+}{P}CH(R)\overset{-}{C}HC(O)R'] \longrightarrow Ph_3P=C(R)CH_2C(O)R' \qquad (2.84)$$

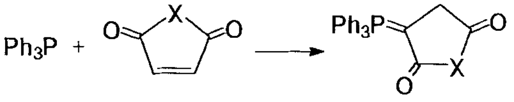
$$R_3P + PhC(O)CH=CHC(O)Ph \longrightarrow R_3P=C[C(O)Ph]CH_2C(O)Ph \qquad (2.85)$$

R=Me, Bu, Ph

Tributylphosphonium benzoyl(phenacyl)methylide (Eq. 2.85)[193]

trans-Dibenzoylethylene (11.11 g) was added to a stirred solution of tributylphosphine (9.51 g) in dichloromethane (20 mL) at 0°C. There was immediate reaction. The deep-brown solution was stirred at 0°C for 15 min and at 20°C for 10 min. The solvent was removed under vacuum and the residue was dissolved in absolute diethyl ether (50 mL) and the solvent was left for several hours at 20°C and then for 2 days at −15°C. 15.7 g of desired ylide, mp 95–97°C, were removed by filtration. Recrystallization of the ylide from benzene–hexane (1:1) gave 13 g of yellow needles, mp 96–97°C.

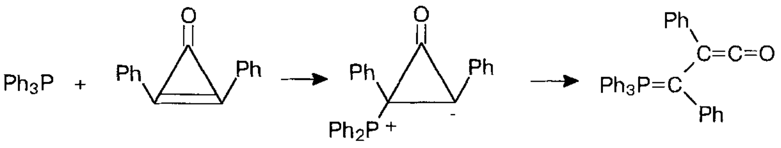
Triphenylphosphine adds maleic anhydride[193,194], and also imides of maleic and fumaric acids[195] with the formation of C-carbonyl-stabilized phosphorus ylides (Eq. 2.86):



(2.86)

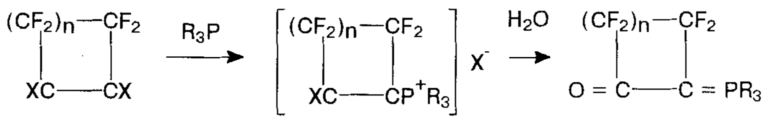
X=O, NR'

Hamada and coworkers showed that reaction of triphenylphosphine with diphenylcyclopropenone in benzene at room temperature for 3 h proceeds with opening of the three-membered ring to afford (triphenylphosphonium benzylide) phenylketene in 92% yield as a stable orange crystalline substance (mp 125–127°C) (Eq. 2.87)[195a]:



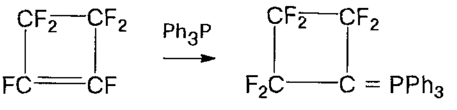
(2.87)

1,2-Dichloroperfluorocycloalkenes and perfluorocycloalkenes react with tertiary phosphines producing vinylphosphonium salts, hydrolysis of which furnishes stable cyclic phosphorus ylides in good yields (Eq. 2.88)[196]. The reaction between triphenylphosphine and perfluorocyclobutane at low temperature leads to the formation in very high yield of triphenylphosphonium perfluorocyclobutenylide, the structure of which was verified by X-ray crystallography (Eq. 2.89)[197]. The reactions of tertiary phosphines with perfluorocycloalkenes is preparatively very simple, as is demonstrated by the preparation of triphenylphosphonium perfluorocyclobutenylide



(2.88)

n=1-3, X-Cl, F; R3P=Ph3P, Ph3(Bu)P, Bu3P



(2.89)

Preparation of triphenylphosphonium perfluorocyclobutenylide (Eq. 2.91)[197]
Perfluorocyclobutene (20 g) was placed in a three-necked flask equipped with a dry-ice–

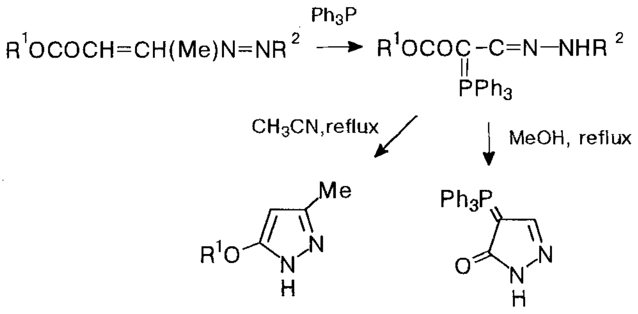
acetone condenser and triphenylphosphine (26 g, 0.1 mol) in diethyl ether (150 mL) was added with stirring. A white precipitate was immediately formed, removed by filtration, and washed with diethyl ether. Yield 42 g.

The reaction of monocyanoacetylene with triphenylphosphine, water or sulfur dioxide gives cyanobetaine which was isolated as a crystalline substance and studied by spectroscopic methods. The hexafluoroisopropylidenevinylamine adds tertiary phosphines with the formation of phosphorus ylides (Eq. 2.90)[198]:

$$R^1CH{=}CHN{=}N(CF_3)_2 \xrightarrow{R^2_3P} R^2_3P{=}C(R^1)CH{=}NC(CF_3)_2 \qquad (2.90)$$

R^1=i-Pr, Ph; R_2=i-Pr, Ph

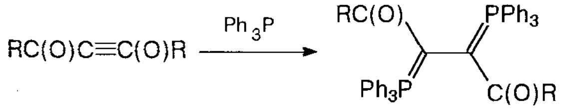
Conjugated azoalkenes react with triphenylphosphine to give stable 1,4-adducts. (Scheme 2.17)[199]. The ylides decompose upon heating to provide a useful synthesis of 5-alkoxypyrazoles and 4-triphenylphosphoranylidene-4,5-dihydrapyrazol-5-ones:



Scheme 2.17

2.2.3.2 Alkynes

Reaction of tertiary phosphines with acetylenecarboxylates leads to the formation of a number of interesting phosphorus ylides.[201-208] The triphenylphosphine adds acetylenedicarboxylate extremely readily to give a variety of products, the structures of which depend on the ratio of reagents and on the reaction conditions. Thus the reaction of 2 equiv. triphenylphosphine with 2 equiv. dimethyl acetylenedicarboxylate or dibenzoylacetylene furnishes 1,2-bis-alkylides in almost quantitative yield (Eq. 2.91)[201,202]:



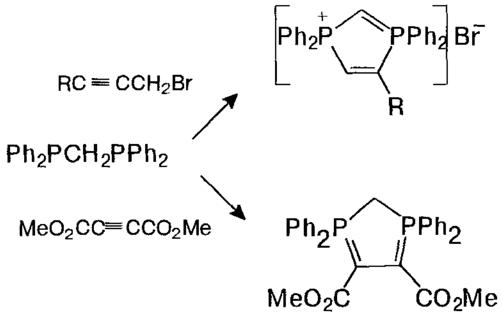
(2.91)

R= MeO, Ph

1,2-Bis-methoxycarbonyl-1,2-bis-triphenylphosphonium ethylidene) (Eq. 2.91)

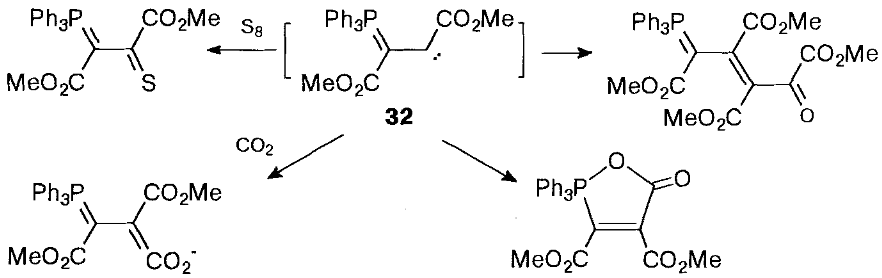
A solution of dimethyl acetylenedicarboxylate (0.7 g) in dry diethyl ether (10 mL) was added dropwise with stirring over 20 min to a solution of triphenylphosphine (3.9 g) in dry ether (30 mL). After a further 10 min a solid (3.5 g) was removed by filtration, washed with methanol (5 mL) and then with absolute ether (20 mL). A pale-brown solid (2.7 g) was obtained. The product was recrystallized from chloroform–ether, mp 220–222°C (dec.) ($\nu_{C=O}$ 1592 cm^{-1}).

Bis(diphenylphosphino)methane reacts with conjugated acetylenes in 1:1 ratio to furnish the 5*H*-diphosphole derivatives (Scheme 2.18)[203–205]:



Scheme 2.18

Zwitterionic intermediates **32** formed by reaction of tertiary phosphines with acetylene dicarboxylates react readily with a second molecule of triarylphosphine, add sulfur or carbon dioxide, or dimerize with the formation of various phosphorus ylides (Scheme 2.19)[203–207]. The intermediates **32** readily adds proton-donating reagents:

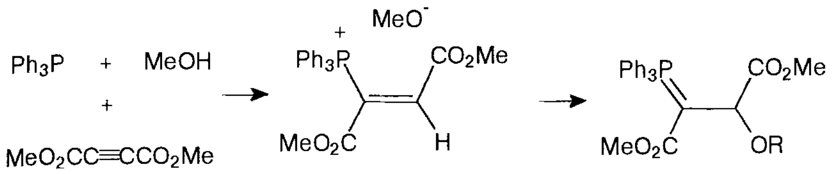


Scheme 2.19

Triphenylphosphine in solution in methanol reacts with dimethylacetylene dicarboxylate to give a stabilized β-alkoxyylide. The reaction proceeds via nucleophilic attack of the phosphine on the acetylene and then of methoxide on the intermediate vinylphosphonium salt by a pathway which involves least build up of negative charge (Eq. 2.92)[207]:

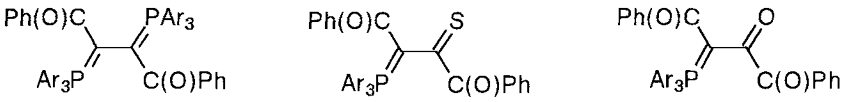
Dimethyl 2-methoxy-3-triphenylphosphoranylidenesuccinate (Eq. 2.92) [207]

Dimethyl acetylene dicarboxylate (1.42 g, 10 mmol) in dry ether (10 mL) was added slowly to a solution of triphenylphosphine (2.88 g, 11 mmol) in ether (25 mL) and dry methanol (5 mL) cooled in ice–salt. Scratching produced white crystals of the P-ylide in quantitative yield; these were removed by filtration and washed with dry ether; mp 153–154°C.



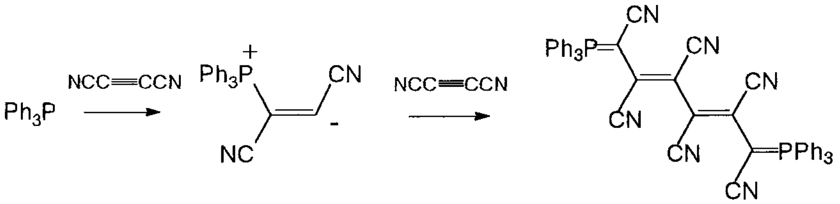
(2.92)

The reaction of triarylphosphines with dibenzoylacetylene proceeds analogously. Depending on the reagent ratio, reaction conditions, presence of proton-donating reagent or reagents (oxidizers, sulfur) capable of interacting with the zwitterionic intermediate, products of ylide or phosphorane structure are formed (Scheme 2.20)[206]:



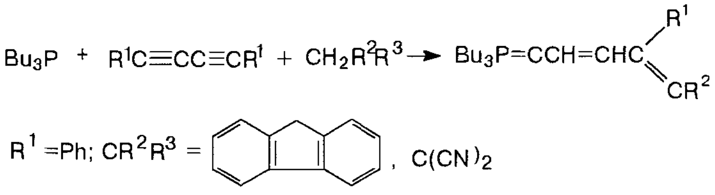
Scheme 2.20

Triphenylphosphine and dicyanoacetylene in 3:2 ratio react readily to produce the stable crystalline alkylidene-1,2-diphosphorane. Reaction proceeds via the formation of a zwitterionic intermediate causing the trimerization of dicyanoacetylene (Eq. 2.93). The formation of zwitterionic a intermediate was successfully proved by chemical reaction:



(2.93)

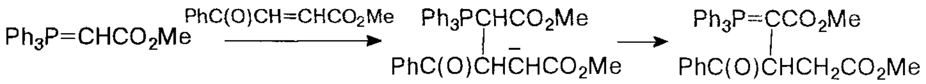
Sprenger and Ziegenbein showed that reaction of conjugated diynes with trialkylphosphines in the presence of compounds with an active methylene group resulted in ylides containing a divinyl group on the ylidic carbon atom (Eq. 2.94)[208]:



(2.94)

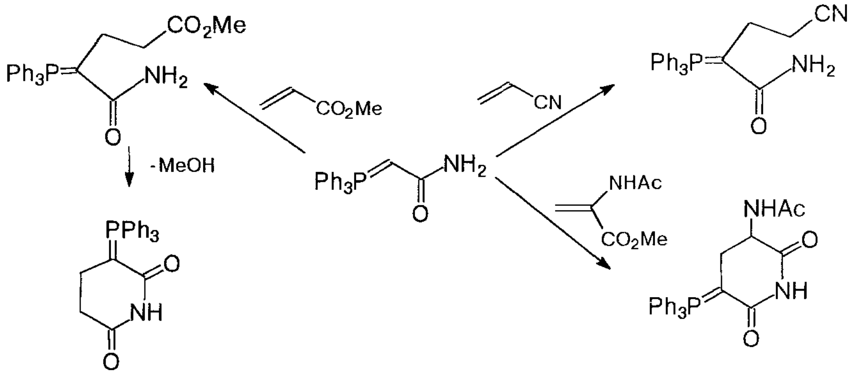
2. 2. 4 Reaction of Tetracoordinate Phosphorus Compounds with Multiple-Bonded Compounds

Phosphorus ylides and some other tetracoordinated phosphorus compounds, react with different Michael acceptors to furnish new phosphorus ylides. Thus, methyl benzoylacrylate adds triphenylphosphonium carbomethoxymethylide to afford a zwitterionic intermediate which readily rearranges to a C-substituted ylide (Eq. 2.95)[209] (see Section 2.3.4.1):



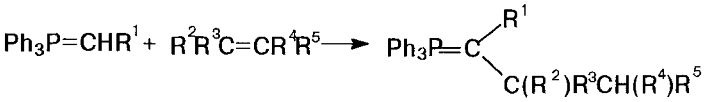
$$Ph_3P{=}CHCO_2Me \xrightarrow{PhC(O)CH{=}CHCO_2Me} \underset{PhC(O)\bar{C}HCHCO_2Me}{Ph_3\overset{+}{P}CHCO_2Me} \longrightarrow \underset{PhC(O)CHCH_2CO_2Me}{Ph_3P{=}CCO_2Me} \qquad (2.95)$$

Amido-stabilized ylides have high nucleophilic reactivity and react with a wide range of Michael acceptors to give new phosphorus ylides (Scheme 2.21)[200a,b]:



Scheme 2.21

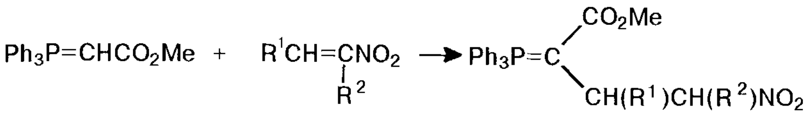
Bestmann and Seng[209] reported that Michael addition of triphenylphosphonium carbomethoxymethylide to methyl benzoylacrylate proceeds by prototropic rearrangement of a betaine intermediate and the formation of a new ylide (Eq. 2.96). Acrylates and methacrylates add the triphenylphosphonium carboethoxymethylide to furnish the triphenylphosphonium carboethoxyalkylides (Table 2.8)[210,211]:



$$Ph_3P{=}CHR^1 + R^2R^3C{=}CR^4R^5 \longrightarrow Ph_3P{=}C\begin{matrix} R^1 \\ C(R^2)R^3CH(R^4)R^5 \end{matrix} \qquad (2.96)$$

33

Triphenylphosphonium carboamidomethylide undergoes Michael addition to methyl acrylate. The acrylic ylide formed readily eliminates methanol to form the glutaramide-ylide which was introduced into the Wittig reaction with aldehydes to furnish alkylideneglutaramide derivatives.[200a,b] Triphenylphosphonium methoxycarbonyl-methylide adds nitroalkenes to form the triphenylphosphonium 1-methoxycarbonyl-3-nitroalkylides in moderate yields (Eq. 2.97)[212, 213]:

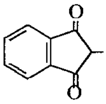


$$Ph_3P{=}CHCO_2Me + R^1CH{=}\underset{R^2}{C}NO_2 \longrightarrow Ph_3P{=}C(CO_2Me)CH(R^1)CH(R^2)NO_2 \qquad (2.97)$$

Table 2.8. Addition of alkenes to phosphorus ylides (Eq. 2.96)

R^1	R^2	R^3	R^4	R^5	Yield of **33** (%)	Ref.
CO_2Me	CO_2Me	H	PhCO	H	92	209
CO_2Me	PhCO	H	MeO_2C	H	92	209
CO_2Me	Ph	H	H	NO_2	23	212
CO_2Me	H	H	Me	NO_2	57	212
CO_2Me	Ph	H	Me	NO_2	48	212
CO_2Me	2-furyl	H	H	NO_2	47	212
CO_2NH_2	H	H	CN	H	-	200
COMe	H	H	COMe	H	76	217
COMe	H	H	COC_6H_4OMe-4	H	78	217
COPh	H	H	COMe	H	89	217
CO_2Me	H	H	COMe	H	91	217
CO_2Me	H	H	CO_2Et	H	87	217
CO_2Me	a		Ph	H	90	218
CO_2Me	**a**		Ph	H	60	218
CO_2Me	**a**		Ph	H	75	218
Ph	**a**		Ph	H	75	218
CO_2Et	H	H	CN	H	90	216
CO_2Et	H	H	CO_2Et	H		210,211
CO_2Et	Ph		H NO_2	H	38	213
CO_2Et	4-FC_6H_4		H NO_2	H	38	213
CO_2Et	1-naphtyl		H NO_2	H	73	213
CO_2Et	1-thiophen		H NO_2	H	18	213
CO_2Me	H		H NO_2	Me	57	213
CO_2Me	Me		H NO_2	H	33	213

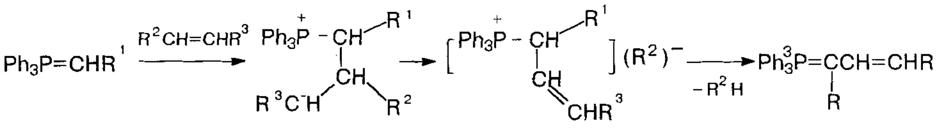
a=



Triphenylphosphonium 3- nitrobutylide (R^1 = H, R^2 = Me) (Eq. 2.97)[212]

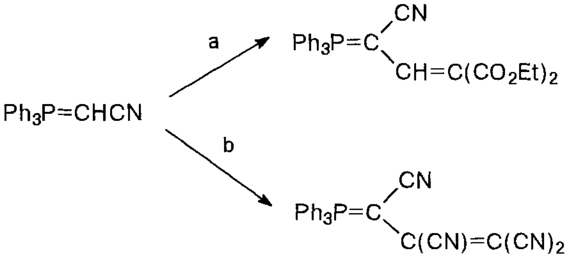
A mixture of 2-nitropropene (3.5 g, 0.04 mol) and Triphenylphosphonium methoxycarbonylmethylide (13.4 g, 0,04 mol) was stirred in absolute toluene (180 mL) for 40 h at 90–100°C. The mixture was then cooled and the toluene was evaporated. Absolute ether (200 mL) was added to the brown residue and the precipitate was removed by filtration. An additional quantity of product was obtained after partial evaporation of the filtrate. Recrystallization of the solid from ethyl acetate provided pure ylide. Yield 57%, mp 161–163.5°C.

The addition of phosphorus ylides to conjugated olefins is accompanied by elimination of an readily leaving group R. The first step of the reaction is also Michael addition, which proceeds with the formation of a betaine containing an anion R^2 which can play the role of base and deprotonate the betaine with the formation of a new phosphorus ylide (Scheme 2.22):



Scheme 2.22

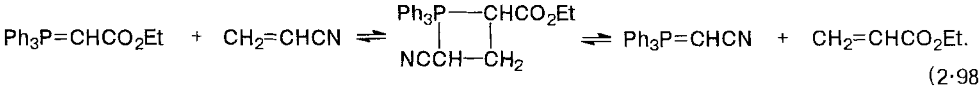
Thus, Trippett and coworkers[175] discovered that reaction of triphenyl-phosphonium cyanomethylide with ethoxymethyl malonate or with tetracyanoethane results in the formation of allylylides. The reaction proceeds with elimination of ethyl alcohol and hydrogen cyanide. Ylide yields are approximately 60% (Scheme 2.23): [214,215]



a: $EtOCH{=}C(CO_2Et)_2$ b: $(NC)_2C{=}C(CN)_2$

Scheme 2.23

The reaction of triphenylphosphonium carbomethoxymethylide with an equimolecular quantity of acrylonitrile in benzene at 90°C proceeds by exchange of the carboethoxymethylide group and the cyanomethylide group to furnish ethyl acrylate and triphenylphosphonium cyanomethylide in 90% yield[216]. This interesting reaction probably proceeds via a four-membered cyclic intermediate formed by cycloaddition of the P=C bond to the C=C bond (Eq. 2.98):

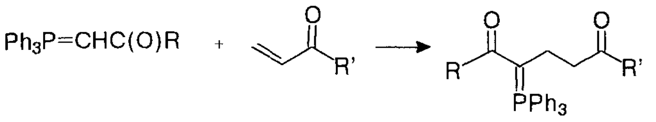


(2·98)

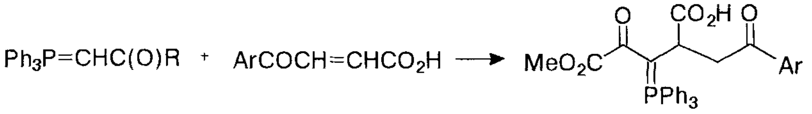
Triphenylphosphonium cyanomethylide [216]

A solution of the triphenylphosphonium carboethoxymethylide (63.0 g, 0.18 mol) and acrylonitrile (9.6 g, 0.18 mol) in benzene (350 mL) was heated under nitrogen in autoclave at 90°C for 16 h. The solvent was removed under reduced pressure and the residue was recrystallized from benzene (400 mL) to furnish colorless crystals. Yield 33.5 g (90%), mp 185–190°C (192–193°C after a second recrystallization).

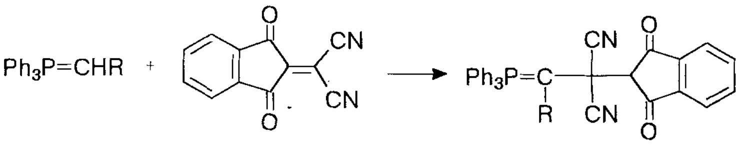
Carbonyl-stabilized ylides react with Michael acceptors to give a phosphorus ylide alkylated at the α-carbon atom (Eq. 2.99-2.101)[200a,217,218]:



(2.99)



(2.100)



(2.101)

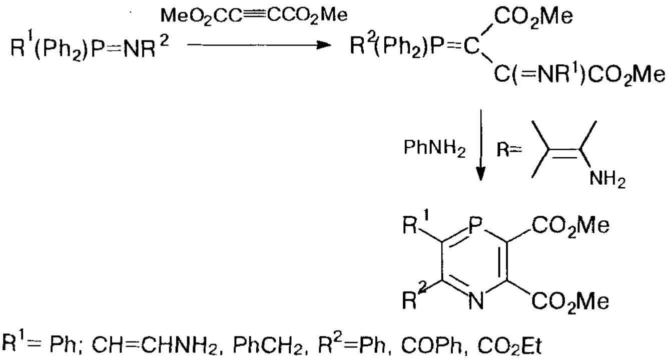
R=Me, Ph, MeO, EtO; R'=Me, C_6H_4OMe

Bruno and coworkers described the addition of phosphorus ylides to α-ketoallenes to give new ylides containing a vinyl group on the α-carbon atom (Eq. 2.102)[214]:

$$Ph_3P{=}CHR' + RC(O)CH{=}C{=}CH_2 \longrightarrow Ph_3P{=}C(R')C(Me){=}CHC(O)R \qquad (2.102)$$

R=Et, R'=CO_2Me; R=i-Pr, R'=CO_2Et; R=Et, R'=CN; R=Et, R'=CN

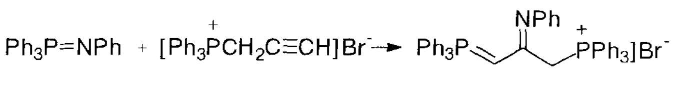
N-phenyl and N-alkoxycarbonyl λ^5-phosphazenes add to acetylenedicarboxylates with the formation of C-substituted phosphorus ylides. Heating of the ylides in boiled acetonitrile resulted in cyclocondensation and loss of aniline to afford 1-aza-4λ^5-phosphinines in excellent yields (Scheme 2.24)[219–222]:



R^1= Ph; CH=CHNH$_2$, PhCH$_2$, R^2=Ph, COPh, CO_2Et

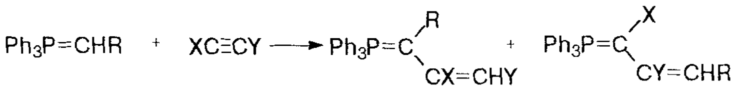
Scheme 2.24

Phosphinimines and prop-2-ynyltriphenylphosphonium bromide react at room temperature to give a phosphorus ylide which undergoes the Wittig reaction with aldehydes (Eq. 2.103)[220,221]:



(2.103)

The reaction of stabilized and semistabilized C-monosubstituted ylides with conjugated alkynes proceeds by Michael addition to afford C-disubstituted ylides **34**,**35** (Eq. 2.104, Table 2.9)[223-226]:



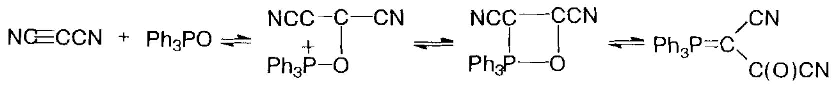
34 **35**

(2.104)

Table 2.9. Reaction of phosphorus ylides with conjugated alkynes (Eq. 2.104)

R	X	Y	Ref
CN	CO_2Me	CO_2Me	175
COR	H	CO_2Me	226
COR	CO_2Me	CO_2Me	225
$CONH_2$	H	CO_2Me	200b
CO_2Et	H	CO_2Et	220a
COMe	H	CO_2Me	223
COPh	H	CO_2Me	223
2-$MeO_2C_6H_4$	CF_3	CO_2Me	224
2-$EtO_2C_6H_4$	C_2F_5	CO_2Me	224
2-$EtO_2C_6H_4$	C_3F_7	CO_2Me	224

Ciganek found a reverse example of the retro-Wittig reaction in which a P–O bond is broken. Dicyanoacetylene reacts with triphenylphosphine oxide at 160°C in a reverse Wittig reaction to give triphenylphosphonium oxalacetonitrilylide in 78% yield. At higher temperatures the direct intramolecular Wittig reaction proceeds with conversion of the ylide into the starting components (Eq. 2.105):



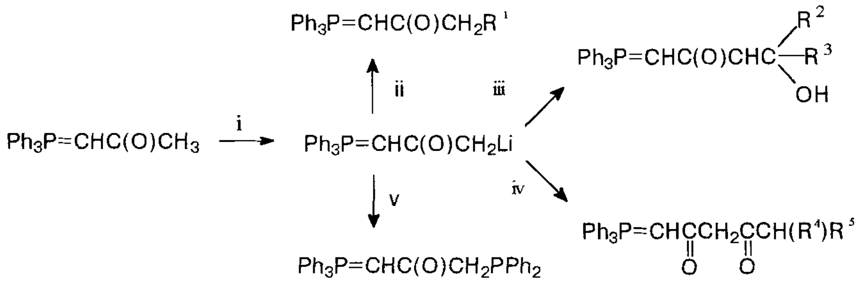
(2.105)

Triphenylphosphonium oxaloacetonitrilylide (Eq. 2.105)[216b]

A mixture of triphenylphosphine oxide (5.73 g, 20.6 mmol), dicyanoacetylene (1.974 g, 20.6 mmol), and benzene (30 mL) in a sealed Carius tube, was heated to 160°C for 12 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel. Elution with dichloromethane–THF (98:2, 1000 mL) gave yellow crystals (6.09 g). Recrystallization from acetonitrile (30 mL) gave 4.69 g of product as yellow crystals, mp 222–223°C. Removal of solvent from the mother liquor and crystallization of the residue from acetonitrile (8 mL) gave an additional 0.97 g product. Overall yield is 78%.

2. 2. 5 Modification of the Side-Chain

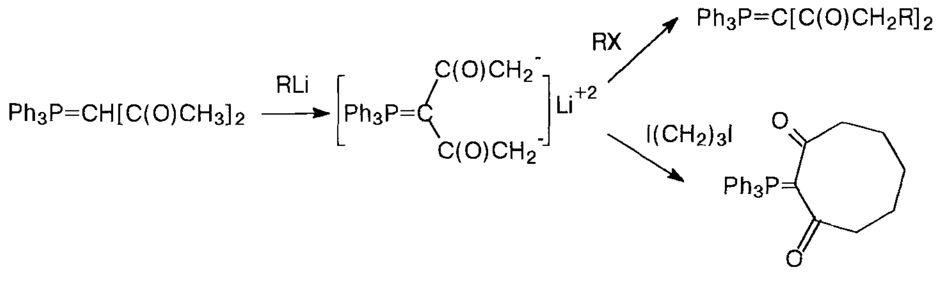
In addition to direct methods of preparation of phosphorus ylides, includingreaction at the ylidic carbon atom, many synthetically interesting phosphorus ylides can be obtained by substitution in a side chain. Thus ketoylides containing an active methylene group can be converted into sodium derivatives by reaction with sodium hydride (Scheme 2.25)[34,72,78,82,89,108,227]. Ylide anions can serve as the initial compounds in the synthesis of other C-substituted phosphorus ylides, because the metal atoms in them are readily substituted by various groups in reactions with electrophiles. Some examples of such reaction are presented in Scheme 2.25 and Table 2.10.



i - RLi; ii - R'X; iii - $R^2R^3C=O$; iv - $R^4R^3CHCO_2Me$; v - Ph_2PCl

Scheme 2.25

Triphenylphosphonium 1-acetyl-2-oxopropylide reacts with excess butyllithium to afford a dilithium derivative which is readily alkylated with mono- and dihaloalkanes to form new acyclic and cyclic diketoylides (Scheme 2.26, Table 2.10)[228].

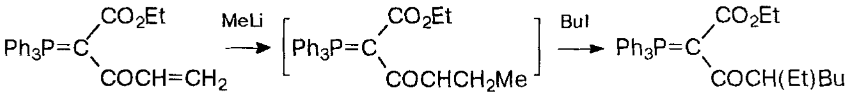


Scheme 2.26

Table 2.10. The reaction of ylide carbanions with nucleophiles (Scheme 2.25; 2.26)

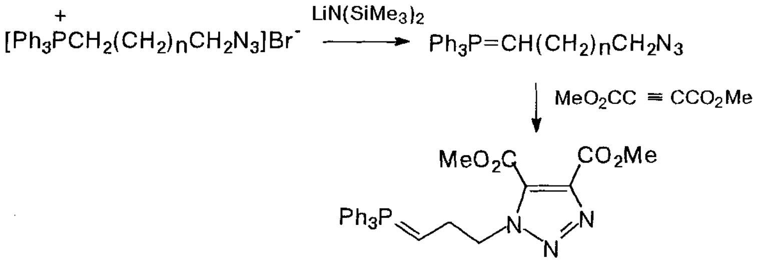
R^1	R^2	R^3	R^4	R^5	Yield,%	Ref.
$PhCH_2$	-	-	-	-	47	228b
$CH_2=CHCH_2$	-	-	-	-	52	228b
C_8H_{17}	--	-	-	-	~100	228a
Ph_2P	-	-	-	-		227
-	Me	H	-	-	43	228b
-	Ph	H	-	-	50	228b
-	Ph	Ph	-	-	81	228b
-	PhCH=CH	Ph	-	-	63	228b
-	-	-	Ph	H	60	228b

Addition of the methyllithium to ketoylides containing a vinyl group in the side-chain gives ylide carbanions which can be used for the preparation of new phosphorus ylides (Eq. 2.106)[229]:



(2.106)

O-Azidoalkyl triphenylphosphonium bromide reacts quantitatively with dimethyl acetylenedicarboxylate to give triazoles. One of the cyclic nitrogen atoms of these heterocyclic compounds bears an alkyl chain substituted by a phosphonium group (Eq. 2.107)[230].

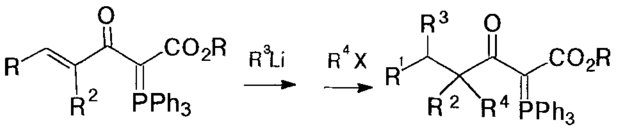


(2.107)

β-Ketoylides can also be alkylated at the γ-non-ylidic carbon atom. Reaction of triphenylphosphonium acetylide with *n*-butyllithium in THF produces a carbanion which is readily alkylated to form new phosphonium ylides which could be used for various transformations. This reaction was used in studies directed towards the synthesis of the polyether macrolide halichondrin B[229b] (Eq. 2.108):

$$Ph_3P{=}CHC(O)Me \xrightarrow{BuLi} Ph_3P{=}CHC(O)CH_2Li \xrightarrow{R'X} Ph_3P{=}CHC(O)CH_2R' \qquad (2.108)$$

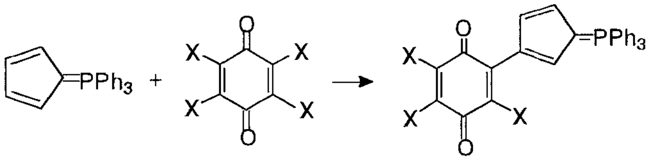
This can be used as an approach to functionalized of α,β-unsaturated carbonyl-containing systems. Addition of nucleophiles to the ylide gives ylide anions, which are readily alkylated with alkyl halides (Eq. 2.109):



1

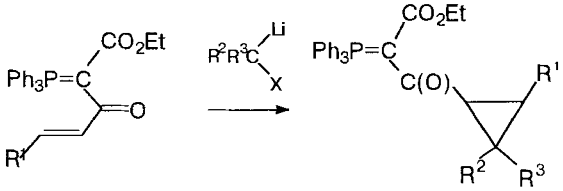
(2.109)

Triphenylphosphonium cyclopentadienylide reacts readily with different electrophiles to give derivatives substituted in cyclopentadienylide ring (Eq. 2.110)[231]



(2.110)

The use of carbenoids to synthesize cyclopropanes from electron-deficient alkenes is generally precluded by preferential reaction of the carbenoid with the alkene-activating substituents. It has been reported that such reactions can be readily achieved in moderate to excellent yields for alkenes carrying β-ketophosphonium ylide substituents because the carbonyl group of such compounds does not react preferentially (Eq. 2.111)[232]:

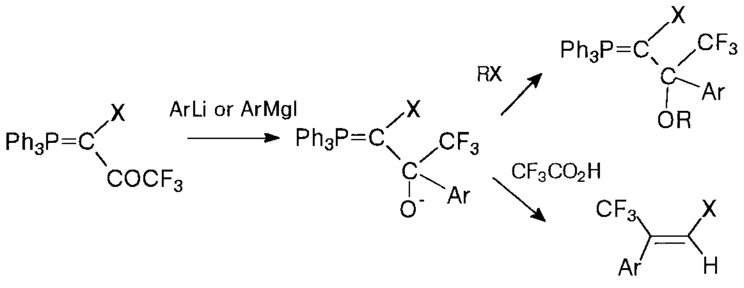


(2.111)

Treatment of keto-ylides with alkyllithiums or Grignard reagents generates the ylide anions; these can be used to prepare of a number of interesting phosphorus ylides. Shen's group reacted these ylide carbanions with different electrophiles to obtain new ylides in very good yields (Scheme 2.27)[233-236]:

2.2.6 Miscellaneous Methods

There are several methods for the synthesis of phosphorus ylides which are not generally applicable but have important preparative applications.



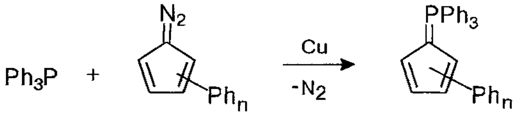
Scheme 2.27

2.2.6.1 Formation from Carbenes

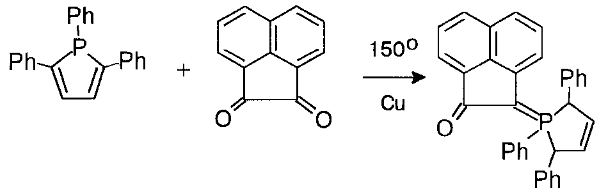
Shtaudinger[237,238] synthesized the first phosphorus ylides by pyrolysis of phosphineazine. The azine, obtained by reaction of triphenylphosphine with diphenyldiazomethane, was heated for 15 min to 195°C and nitrogen furnishing triphenylphosphonium diphenylmethylide (Eq. 2.112):

$$\overset{:}{Ph_3P} + Ph_2CN_2 \longrightarrow Ph_3P{=}NN{=}CPh_2 \xrightarrow[-N_2]{195^\circ C} Ph_3P{=}CPh_2 \tag{2.112}$$

Many years later several groups proposed the preparation of phosphorus ylides by heating triphenylphosphine with diazo compounds in the presence of a copper catalysts[239–243]. Effective catalysts of this reaction are copper bronze[242] and bis (hexafluoroacetylacetonate)copper[243]. For example, heating of diazacyclopentadienes with triphenylphosphine at 150–160°C for 10–60 min furnishes triphenylphosphonium cyclopentadienylides (Eq. 2.113) and phosphole ylide (Eq. 2.114) in 26–41% yields (Eq. 2.115)[243]:



(2.113)



(2.114)

Reaction of triphenylphosphine with sulfonium dicyanomethylide at 130–140°C is followed by transfer of the ylide fragment from sulfur to phosphorus to produce dicyanomethylide and sulfide[244]. Reaction probably proceeds via thermal dissociation of the sulfur ylide to form a carbene which then was trapped by the more nucleophilic triphenylphosphine (Eq. 2.115):

$$R_2S{=}C(CN)_2 \longrightarrow [:C(CN)_2] \xrightarrow{Ph_3P} Ph_3P{=}C(CN)_2 + R_2S \qquad (2.115)$$

Phosphorus ylides were obtained from iodine ylides as starting compounds. Phenyliodonium ylides react with triphenylphosphine when heated under reflux benzene in the presence of the acetylacetonate copper as catalyst to afford phosphonium ylides in high yield (Eq. 2.116)[245]:

$$PhI{=}C(SO_2R)_2 + Ph_3P \longrightarrow Ph_3P{=}C(SO_2R)_2 + PhI \qquad (2.116)$$

2.2.6.2 Phosphorylation of Compounds with an Active Methylene Group

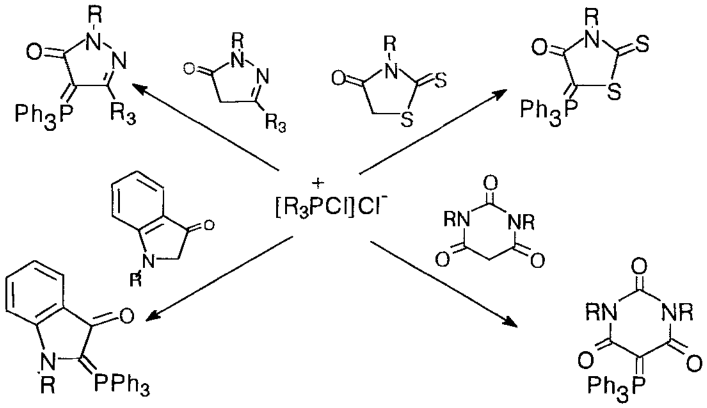
Compounds with an active methylene group react readily with triphenyldichlorophosphorane in the presence of triethylamine to form phosphorus ylides in very good yields. The reaction consists in the phosphorylation of the active methylene group with subsequent dehydrochlorination of the phosphonium salt formed. Although this is one of the most simple methods for the preparation of phosphorus ylides, unfortunately it enables the preparation of highly stabilized, and generally unreactive ylides, only which do not undergo the Wittig reaction (Eq. 2.117)[246,247]:

$$Ph_3PCCl_2 + CH_2RR' \xrightarrow{Et_3N} Ph_3P{=}CRR' \qquad (2.117)$$

$R = MeCO, PhCO, MeO_2C, EtO_2C, CN, PhSO_2, CH_2C{=}CHSO_2$

Substituted 3-oxopyrazolines, 4-oxo-2-thionothiazolidines, rodanines, 2-oxo-2,3-dihydroindoles and barbituric acid derivatives react with triphenyldichlorophosphorane providing the corresponding ylides in 50–98% yields (Scheme 2.28)[248]:

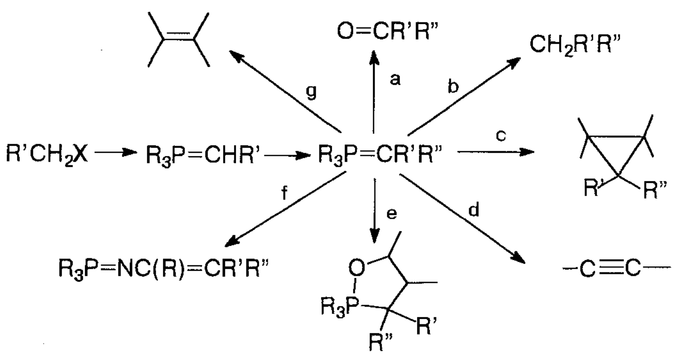
So, phosphonium ylides are accessible compounds which can be obtained by simple methods from cheap chemical reagents. The high accessibility of phosphorus ylides serves as the reason for the intensive studies of their chemical properties that has led to the wide application of ylides in preparative chemistry and in industrial fine organic synthesis.



Scheme 2.28

2.3 Chemical Properties

In recent years the chemistry of C,P-carbon-substituted phosphorus ylides has been extensively developed—the chemical properties of the compounds have been studied in detail and the range of their practical application in organic synthesis have been discovered. The chemical properties of C,P-carbon-substituted are extremely diverse, because of the variety of the properties of the substituents at the phosphorus and carbon atoms of the P=C group and their effects on the electron density distribution in ylide molecules. Because of their unique molecular and electronic structure, phosphorus ylides undergo a wide variety of reactions (Scheme 29):



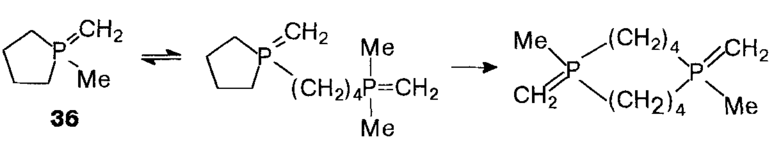
a) oxidation; b) hydrolysis; c) $R_2C{=}CR_2$; d) R′ = RC(O), intramolecular Wittig reaction; e) oxirane; f) RC≡N; g) $R_2C{=}O$, intermolecular Wittig reaction

Scheme 2.29

Some of these are typical of the carbanion nature of ylides in general. The phosphonium group has little effect on such reactions, taking part only as electron-withdrawing substituent attached to carbanion. Other reactions depend on the unique phosphorus ylide structure and involve both the carbanion and phosphonium parts of the ylide. C,P-Carbon-substituted phosphorus ylides attract particular interest as reagents for organic synthesis, and thus find increasing application in laboratory practice and industry. The most important and useful reaction of phosphorus ylides is certainly their reaction with carbonyl compounds, which enables the preparation of alkenes. This reaction is reviewed in Chapter 6. Other reactions of phosphorus ylides, which are important synthetic tools in organic synthesis are discussed in this chapter These reactions lead to the formation of numerous interesting types of organic compound—ketones, hydrocarbons, cyclopropanes, acetylene derivatives, 1,2λ^5-oxaphospholanes, iminophosphoranes, and others (Scheme 2.29):

2.3.1 Stability

In contrast with the ylides of other heteroatoms, phosphorus ylides do not usually show propensity for spontaneous thermal decomposition. Most phosphorus ylides are thermally comparatively stable compounds. Many can be purified by crystallization from indifferent organic solvents or distilled under reduced pressure. The most stable are ylides bearing electron-accepting substituents at the α carbon atom, which reduces the basicity and the nucleophilicity of the ylides. Stabilized ylides withstand the high temperatures, and the moisture and oxygen of the atmosphere. For example, triphenylphosphonium carboethoxymethylide does not decompose on heating for 40 h at 180°C[250]. Because non-stabilized ylides are easily oxidized and hydrolyzed, they are usually used for farther transformations without isolation from reaction solutions, although simple non-stabilized phosphorus ylides have been isolated and studied by different physical methods. Thus, triphenylphosphonium methylide was isolated as a crystalline orange substance,[48] trialkylphosphonium alkylides were purified by distillation under vacuum and obtained as colorless liquids very reactive to moisture and oxygen. Unstable phosphorus ylides undergoing interesting transformations are also well-known. The five-membered cyclic phosphorus ylide **36** below, for instance, dimerizes easily at 20°C (Eq. 2.121)[251]:

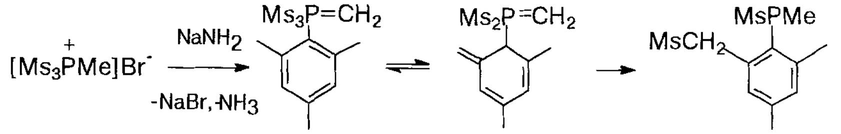


36

(2.121)

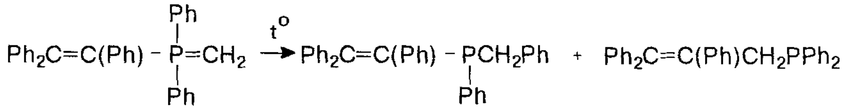
In contrast with nitrogen and sulfur ylides, which readily undergo Stevens rearrangement to produce the corresponding tertiary amines. and sulfides, there are few reports of a similar reactions of their phosphorus analogs[252]. Although phosphorus ylides rarely undergo the Steven's rearrangement to form trivalent phosphorus compounds, several examples of such reactions have been described. For instance, trimesitylphosphonium methylide easily enters into the Steven's rearrangement immediately after its formation (Eq. 2.122)[253,254]. Triarylphosphonium alkylides undergo Steven's rearrangement in the presence of nickel-complex catalysts (Eq.

2.123). Maercker and coworkers[255] showed that 2,2,1-triphenylvinyldiphenylphosphonium methylide rearranges into trivalent phosphorus compounds when heated to 200°C in tetralin (Eq. 2.124). An interesting example of the Steven's rearrangement of 1-fluoren-9-ylidene-1,2,5-triphenyl-λ^5-phosphole was described by Gilheany.[256] When heated under reflux in toluene the cyclic phosphorus ylide underwent virtually quantitative conversion into an isomeric trivalent phosphorus product (Eq. 2.125):



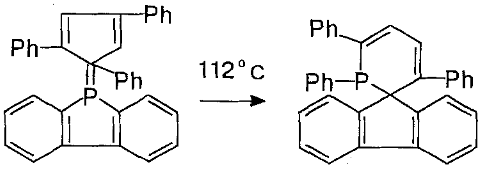
(2.122)

$$R_3P{=}CHR' \xrightarrow{Ni(C_6H_{12})_2} R_2PCH(R)R' \qquad R{=}Ph,\ PhCH_2;\ R'{=}H,\ Me,\ Et \qquad (2.123)$$



$$Ph_2C{=}C(Ph)-\underset{Ph}{\overset{Ph}{P}}{=}CH_2 \xrightarrow{t^o} Ph_2C{=}C(Ph)-\underset{Ph}{P}CH_2Ph + Ph_2C{=}C(Ph)CH_2PPh_2$$

(2.124)



(2.125)

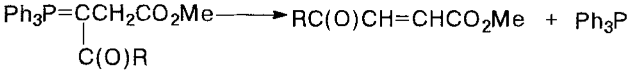
2.3.2 Transformations Accompanied by Cleavage of the P=C Bond

The ylidic P=C bond is relatively stable on heating, despite of the high chemical activity of phosphorus ylides. Nevertheless on heating or photolysis, P-ylides can be cleaved at the phosphorus–carbanion (P=C) bond. The cleavage reaction of P-ylides is useful in synthetic chemistry. Hydrolysis, oxidation, reduction, photolysis and electrolysis can be used for interesting transformation of P-ylides or to remove the phosphorus group from compounds resulting from initial P-ylides.

2.3.2.1 Thermolysis

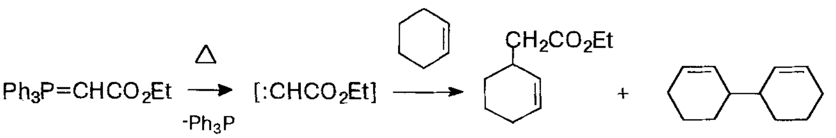
Phosphorus ylides undergo several types of thermal decomposition reaction, the most important of which are the thermal cleavage of the P=C bond with generation of carbenes, the intramolecular Wittig reaction, and skeletal rearrangements.

The phosphorus ylides are generally more stable than the ylides of other elements. They do not show such clear propensity to decompose with generation of carbenes as, for example, nitrogen and sulfur ylides[252]. Nevertheless on heating or, sometimes, at room temperature some phosphorus ylides decompose with elimination of the triphenylphosphine to generate carbenes. Thus, ylides containing hydrogen atoms on the β carbon and electron-accepting substituents which increase mobility of these atoms are cleaved on heating with the formation of triphenylphosphine and olefin[159,257]. (Eq. 2.126). This reaction is similar to the thermal Hoffmann decomposition of quaternary ammonium salts:



$$\underset{\displaystyle C(O)R}{Ph_3P{=}CCH_2CO_2Me} \longrightarrow RC(O)CH{=}CHCO_2Me + Ph_3P \qquad (2.126)$$

Another interesting example of such reactions was described by Nagao and coworkers[250]. They showed that triphenylphosphonium carboethoxymethylide at decomposes at 180°C, with cleavage of the P=C ylide bond, to afford carboethoxycarbene which was trapped with the cyclohexene (Eq. 2.127):



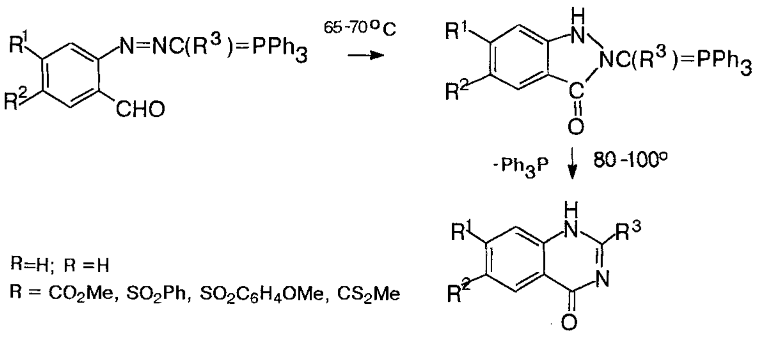
(2.127)

At 20°C trimethylphosphonium allylylide eliminates ethylene to form trimethylphosphonium methylide (Eq. 2.128)[258]. Tri-*tert*-butylphosphonium methylide decomposes at room temperature to afford isobutylene and di-*tert*-butylmethylphosphine (Eq. 2.129)[259]:

$$Me_3P{=}CHCH{=}CH_2 \longrightarrow Me_3P{=}CH_2 + CH_2{=}CH_2 \qquad (2.128)$$

$$t\text{-}Bu_3P{=}CH_2 \longrightarrow t\text{-}Bu_2PMe + Me_2C{=}CH_2 \qquad (2.129)$$

The heating of O-formylarylazomethylides to 65–70°C affords ylides which on further heating at 80–100°C are converted into 4-oxo-1,4-dihydroquinazolines and Ph_3P (Scheme 2.30)[260]:

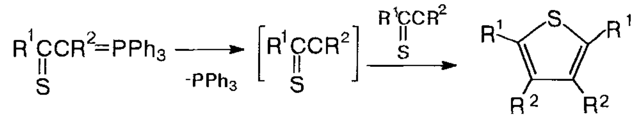


Scheme 2.30

Wittig reported that the ylide–phosphonium salt decomposes immediately after formation from bis(triphenylphosphonium)ethane (Eq. 2.130)[261]:

$$[\overset{+}{P}h_3PCH_2CH_2\overset{+}{P}Ph_3]Br^{2-} \longrightarrow [Ph_3P{=}CHCH_2\overset{+}{P}Ph_3]Br^- \xrightarrow[-\ PPh_3]{} [Ph_3\overset{+}{P}CH{=}CH_2]Br^- \tag{2.130}$$

Heating of triphenylphosphonium thioacylalkylylides to melting results in the formation of substituted thiophenes. The mechanism of the reaction probably involves the elimination of triphenylphosphine and [2+3]-cycloaddition of the formed thiocarbonyl carbene to a second molecule of phosphorus ylide. Yields of thiophenes are 37–73% (Eq. 2.131)[262]:

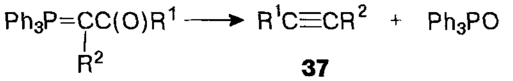


(2.131)

R^1 =Ph, 2-thienyl, 4-t-BuC_6H_4; R^2=H, Me

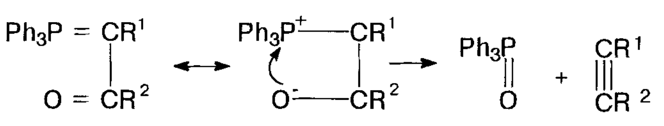
Intramolecular Wittig-Trippet Reaction

The most important thermal transformation of phosphorus ylides is the intramolecular Wittig reaction of α-carbonyl-substituted phosphorus ylides—after loss of triphenylphosphine oxide this results in the formation of alkynes **37** (Eq. 2.132):



$$\underset{R^2}{Ph_3P{=}\overset{|}{C}C(O)R^1} \longrightarrow \underset{\mathbf{37}}{R^1C{\equiv}CR^2} + Ph_3PO \tag{2.132}$$

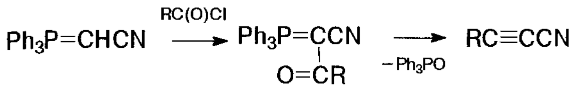
The first example of the intramolecular Wittig reaction was described by Trippett and Walker[146]. They found that at 300°C triphenylphosphonium α-benzoylbenzylide eliminates triphenylphosphine oxide to afford diphenylacetylene in good yield (Eq. 2.133)[262b,262c]:



R^1=Ph, CO_2Et; R^2=Ph

(2.133)

Numerous examples of the intramolecular Wittig reaction for the preparation of disubstituted acetylenes have been described in recent years[262-287]. The intramolecular Wittig reaction of C-carbonyl-substituted ylides, bearing an electron-accepting group R on the α-carbon atom, in particular $C(O)R$[122], CO_2R[263,264], CN[265], $Ph_2P(O)$[268], SR[267b], SeAr[267a], and Ph[146,162,266] furnishes acetylene derivatives in very good yields (Table 2.11). Rao and coworkers[269] obtained cyanoacetylenes by thermolysis of cyanoketomethylides under vacuum (Eq. 2.134):



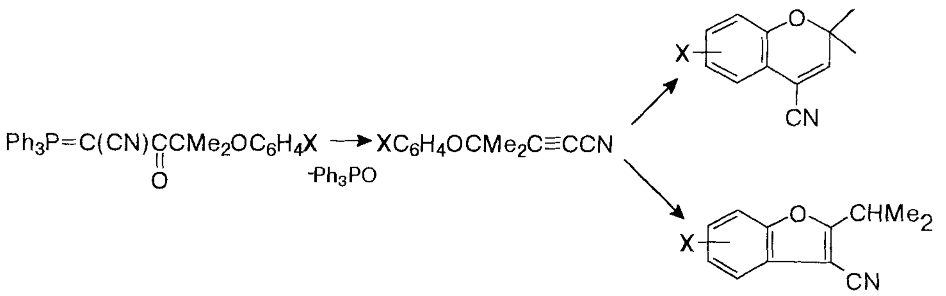
$$Ph_3P{=}CHCN \xrightarrow{RC(O)Cl} Ph_3P{=}\underset{O=CR}{C}CN \xrightarrow[-Ph_3PO]{} RC{\equiv}CCN \qquad (2.134)$$

R=1-adamantyl, RCH=CH, XC_6H_4, $XC_6H_4OCH_2$; X=H, AlkO, Cl

Thermolysis of triphenylphosphonium 2-phenoxypropionylcyanomethylides under vacuum at 260–270°C follows by intramolecular Wittig reaction and the Claisen rearrangement to afford intermediate propargyl esters **38** which, depending on the substituents X on the benzene ring, are readily converted into 1-benzopyrans or benzofurans. 1-Benzopyrans were obtained in yields of 50–58%, when X = H, 2-MeO, 4-Me, or 2-Me (Scheme 2.31)[269]:

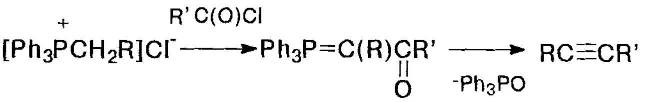
Table 2.11. Synthesis of alkynes **37** by thermolysis of *β*-oxidoylides (Eq. 2.134)

R	R'	Conditions		Yield,%	Ref
		t° C	p, mmHg		
Ph	Ph	300	10	34-64	262
Ph	Me, Ph	250-280	0.01	67-90	267b
Ph, Bu	Me, Ph,CN,CO_2Et	280	0.35	9-30	262b
H	Me, Et, n-Bu, t-Bu, Ph	750	0.01	78-82	272a
Me	Me	250-280	0.01	88	267b
Me	2-Thienyl	750	0.01	64	272a
Pr	c-C_6H_{11}	750	0.01		272a
H,Alk,Ph	Ph	500-700	0.1-0.005	49	272b
CF_3	C_6H_4R R=H,Me,MeO,Cl,NO_2)	280-410	10	40-85	266
C_6F_5	$(CF_2)_3Cl$; C_nF_{2n+1}, n=1-7	230-260	12	85-96	273a
CF_3	NEt_2	240	10	62-95	283
CN	$ClCF_2$, $Cl(CF_2)_n$, n=3,5	280	10	53-85	265
CN	n-$C_3F_7OCF(CF_3)$	280	10	77	265
CN	C_nF_{2n+1},n=1-3	220-260	10-15	50-82	260
PhCO	PhCO, MeO_2C	500	FVP	23-40	272c
MeCO	MeO_2C	500	FVP	67	272c
MeO_2C	Me, Pr,c-C_5H_{11}, Ph, $C_{13}H_{27}$, 2-Furyl	220-250	0.05-12	65-85	263,264
MeO_2C	C_5H_4X, X=H, Me, Cl, MeS	500	0.1-0.001	66-90	271a,b
MeO_2C	2-Furyl; l,2-Thienyl; c-C_6H_{11}	750	0.1-0.001	16-66	271b
EtO_2C	C≡CPr	500	0.1-0.001	37	271a
$MeSCOCH_3$	C_nF_{2n+1}, n=27	230-260	12	90-95	273b,c
EtO_2C	EtO_2C	500	FVP	70	272c
EtO_2C	2-Thienyl,2-Furyl, 1-Naphtyl	500-700	0.1-0.005	30-81	22,272b
CHO	CF_6	220-260	10	60	274
OPh	C_nF_{2n+1}	250-270	10	28-35	276
SMe	Ph, CF_3	230	0.005	74	267a,b
SPh	Me, t-Bu, C_5H_{11}, Ph	230	0.005	41-77	267b
SePh	C_6H_4X, X=H, Me, MeO, Cl, NO_2	210	0.005	55-83	267a
Cl, Br	Ph, t-Bu	800	0.001	50	275
$P(O)(OPh)_2$	C_nF_{2n+1},n=1-3	220	10^{-5}	78-85	276



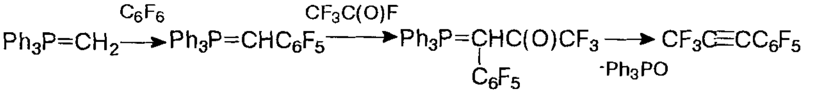
Scheme 2.31

The reaction of phosphorus ylides with acylating reagents in a biphasic system furnishes keto-ylides, the thermolysis of which leads to the formation of acetylene derivatives in good yields (Eq. 2.135)[126]:

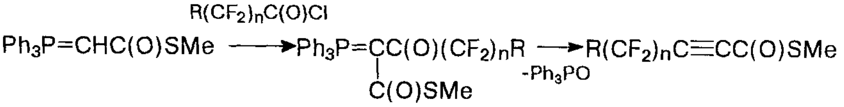


$$[Ph_3\overset{+}{P}CH_2R]Cl^- \xrightarrow{R'C(O)Cl} Ph_3P{=}C(R)\underset{\underset{O}{\|}}{C}R' \xrightarrow[-Ph_3PO]{} RC{\equiv}CR' \qquad (2.135)$$

Shen[273a] obtained ylides bearing pentafluorophenyl and trifluoromethylacetyl groups on the α-carbon atom by consecutive reaction of triphenylphosphonium methylide with hexafluorobenzene and trifluoroacetyl-fluoride. The thermolysis of this ylide at 200°C under vacuum furnishes perfluoroacetylene derivatives in high yield (Eq. 2.136).The thermolysis of fluoro-containing thioester ylides **39** led to the formation of polyfluoroacetylenecarboxylic acids in yields of 90–95% (Eq. 2.137)[273b]: The methodology of these preparations is comparatively simple.



$$Ph_3P{=}CH_2 \xrightarrow{C_6F_6} Ph_3P{=}CHC_6F_5 \xrightarrow{CF_3C(O)F} Ph_3P{=}\underset{\underset{C_6F_5}{|}}{C}HC(O)CF_3 \xrightarrow[-Ph_3PO]{} CF_3C{\equiv}CC_6F_5 \qquad (2.136)$$



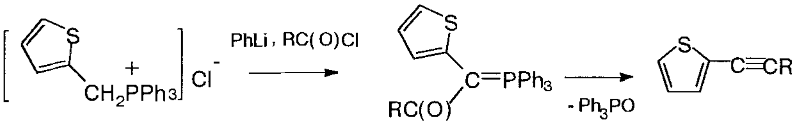
$$Ph_3P{=}CHC(O)SMe \xrightarrow{R(CF_2)_nC(O)Cl} Ph_3P{=}\underset{\underset{C(O)SMe}{|}}{C}C(O)(CF_2)_nR \xrightarrow[-Ph_3PO]{} R(CF_2)_nC{\equiv}CC(O)SMe \qquad (2.137)$$

39

General method of preparation of perfluoro-1-pentafluorophenyl-1-alkynes (Eq. 2.137)[273b]
Triphenylphosphonium α-(perfluoroalkanoyl)perfluorobenzylide was pyrolyzed in a distillation vessel at 200–260°C (2 mmHg). The pyrolyzate was collected into a dry ice–ethanol trap. Redistillation afforded the pure product. Yield 83% (R = CF_3), 65% (C_3F_7), 75% (C_7F_{15}), 51% [$(CF_2)_3Cl$], 71% [$(CF_2)_5Cl$].

Methyl pentafluorothiopent-2-ynoate (Eq. 2.137; R = F, n = 2)[273b]
The ylide **39** (3.0 g, 6 mmol) was heated at 70°C for 2 h under nitrogen and then pyrolyzed at 190–220°C for 2 h under nitrogen at reduced pressure (p = 1 mmHg). Pyrolyzate was collected into a dry ice–ethanol trap. After redistillation the alkyne was obtained in yield of 1.2 g (92%), bp 122°C.

The combination of the intramolecular Wittig reaction with quaternization of triphenylphosphine by reaction with haloalkyl R^1CH_2X or acylation of a phosphorus ylide with $R^2C(O)Cl$ enabled the preparation of alkynes containing heterocyclic rings on the α-carbon atoms (Eq. 2.138)[277]:

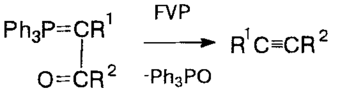


(2.138)

Conventional pyrolysis of $\beta,\beta,\gamma,\gamma$-tetraoxophosphorus ylides by distillation at 200°C gave trioxoalkynes (Eq. 2.139)[285]:

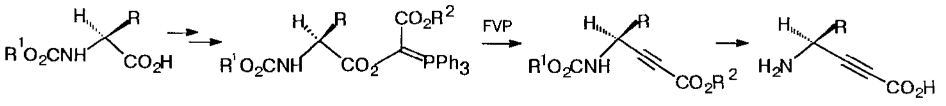
$$Ph_3P{=}CHC(O)C(O)R + ClCOCOR' \rightarrow Ph_3P{=}C(COCOR)_2 \rightarrow RCOC{\equiv}CCOCOR \qquad (2.139)$$

Pyrolysis of β-oxoylides containing R′ = H or Alkyl on the ylidic carbon atom usually furnishes alkynes in moderate yields. Use of flash-vacuum pyrolysis (FVP) enables the preparation of the corresponding alkynes in good yields[278]. According to this methodology short-term heating of the α-carbonyl-substituted phosphorus ylides to 750°C under vacuum (0.01–0.001 mmHg) produces alkynes, which were collected into a cooled trap[280a]. Under optimum conditions high-temperature FVP proceeds without formation of triphenylphosphine and allenes, which are formed by low-temperature thermolysis (Eq. 2.140)[280a]:

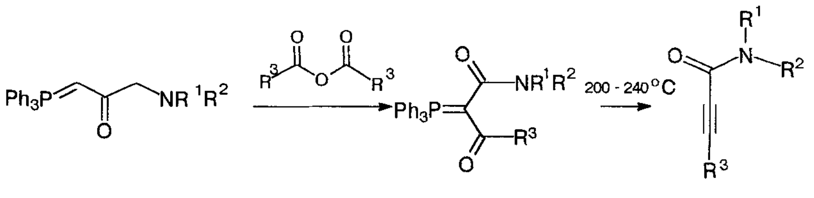


$$\begin{array}{c}Ph_3P{=}CR^1\\ |\\ O{=}CR^2\end{array} \xrightarrow[-Ph_3PO]{FVP} R^1C{\equiv}CR^2 \qquad (2.140)$$

Aitken and coworkers[280b] reported the FVP of stabilized ylides as a method for overall conversion of carboxylic acids, including amino acids, into homologous acetylenic esters and terminal alkynes. A wide range of alkoxycarbonyl protected amino acids have been converted into the protected acetylenic amino acids in good yield and without significant racemization (Eq. 2.141). The latter compounds lead to a wide variety of chiral amines and amino acids as potential selective enzyme inhibitors and components of modified peptide structures[280b]:



(2.141)



(2.142)

Shen and Gao reported the preparation of perfluoroalkynoamides in 62–95% yields by pyrolysis of perfluoroalkyl phosphorus ylides (Eq. 2.142) [283]:

Different acetylene derivatives were prepared by Aitken's group in good yield and regioselectivity (Eq. 2.143–146)[271a,b,272a,b,284a–c]. FVP of 1,2,4-trioxo-3-triphenylphosphorinylidenebutane derivatives results in selective extrusion of Ph_3PO exclusively across the 2,3 position to give diacylalkynes in yields of 44–82% (Eq. 2.145)[272b,284b,c]:

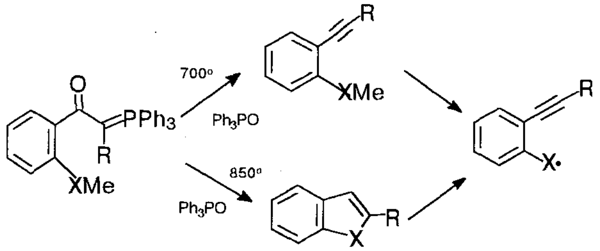
$$Ph_3P{=}C(R^1)C(O)CH{=}CHR^2 \xrightarrow[-Ph_3PO]{FVP} cis\text{-} + trans\text{-}R^1C{\equiv}CCH{=}CHR^2 \qquad (2.143)$$

$$Ph_3P{=}C(CO_2Et)COR \xrightarrow{FVP} RC{\equiv}CCO_2Et \longrightarrow RC{\equiv}CH \qquad (2.144)$$

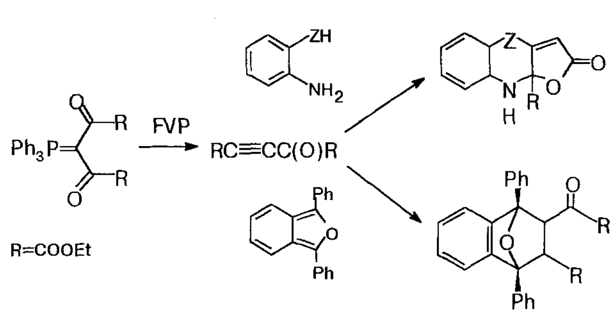
$$Ph_3P{=}C(COR)COCOR \xrightarrow{500^\circ C} RCOC{\equiv}CCOR' \qquad (2.145)$$

$$Ph_3P{=}C(COCOR)_2 \xrightarrow{FVP} RC(O)C(O)C{\equiv}CC(O)C(O)R' \qquad (2.146)$$

The FVP of phosphorus ylides containing alkynylphenoxy, phenylthiophenyl, or α–methoxybenzoyl groups proceeds with the generation of the corresponding radicals; these undergo tandem cyclization leading to the formation of heterocyclic compounds[82]. At 850°C the FVP of β–oxoylides bearing an α–methoxybenzoyl group is accompanied by loss of Me and cyclization of the resulting radicals with the formation of 2-substituted benzofurans or benzothiophenes (Scheme 2.32)[287].

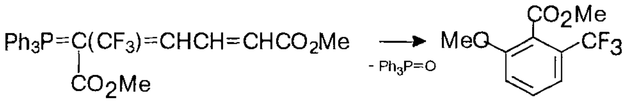


Scheme 2.32



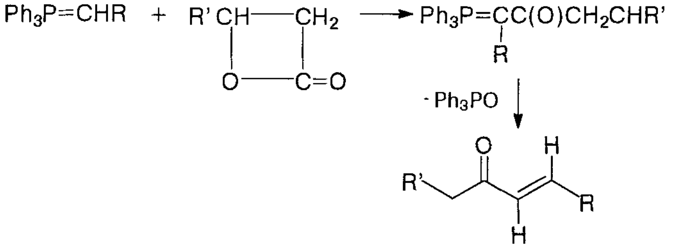
Scheme 2.33

Alkynes prepared by FVP can be then introduced into different cyclization reactions. Thus, diethyl 2-oxopentynedioate was prepared by FVP of bis(ethoxalyl) methylide and then used as a reactive building block in a Diels–Alder reaction (Scheme 2.33)[286]. Recent years have seen the development of new directions of thermolysis of C-substituted ylides. Ding and coworkers, for example, found that heating conjugated ylides under reflux in xylene is accompanied by elimination of triphenylphosphine oxide to provide methyl benzoate derivatives (Eq. 2.147)[279] :



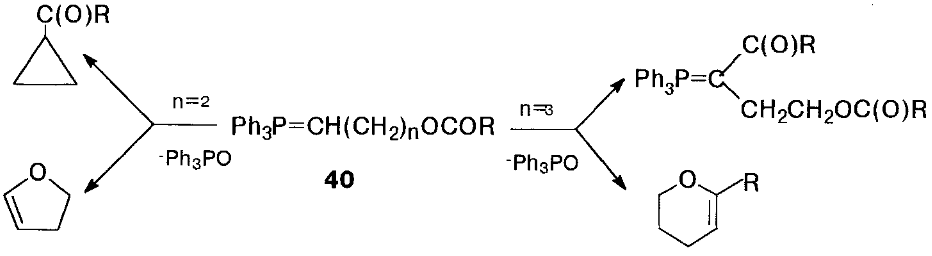
(2.147)

δ–Hydroxy-β-ketoylides, prepared from ylides and propiolactone, eliminate phosphine oxide on heating to produce α,β–unsaturated ketones in good yields (Scheme 2.34)[288]:



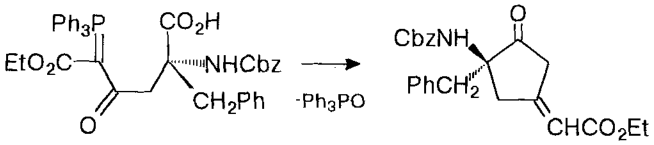
Scheme 2.34

Heating triphenylphosphonium acyloxyalkylides **40** ($n = 2$) under reflux in toluene gave 2,3-dihydrofurans, whereas in boiled *tert*-butanol ylides **40** converted to cyclopropylketones[289,290]. Similar treatment of ylide **40** ($n = 3$) leads to the formation of α–acylated ylides in *tert*-butanol and of the 3,4-dihydro-2*H*-pyrans in toluene (Scheme 2.35)[289,290]:



Scheme 2.35

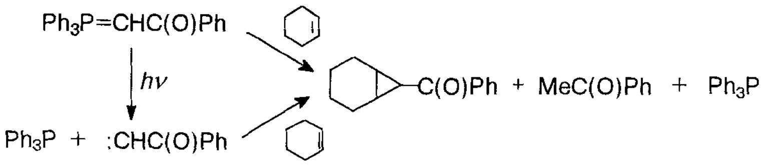
β–Ketoylide-substituted phenylalanine in boiled THF readily eliminates phosphine oxide to afford lactones (Eq. 2.148)[291] :



(2.148)

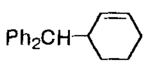
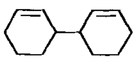
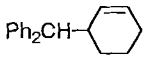
2.3.2.2 Photolysis

The photolysis of phosphorus ylides proceeds with cleavage of the P=C bond to produce carbenes (Table 2.12)[293a]. Thus, the irradiation of triphenylphos-phonium benzylide at $h\nu > 3000$ A in a Pyrex tube, as was reported by Silva and coworkers, proceeds with the formation of triphenylphosphine and singlet benzoylcarbene. The latter was trapped with cyclohexene to afford 7-norcarylphenylketone (Scheme 2.36)[292–294]:



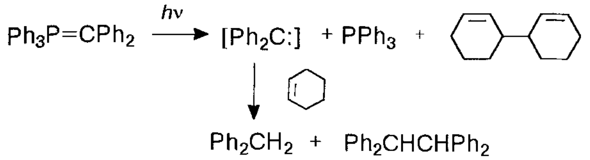
Scheme 2.36

Table 2.12 Photolysis of triphenylphosphonium diphenylmethylide in cyclohexane solution

Product	Yield (%)		Ref
	Quartz tube	Pyrex tube	
PhH	78	5	293,
Ph_2CH_2	6	-	293
	57	56	293
$Ph_2CHCHPh_2$	10	-	293
Ph_3P	0[a]	90	293
	-	-	293
	11	-	293

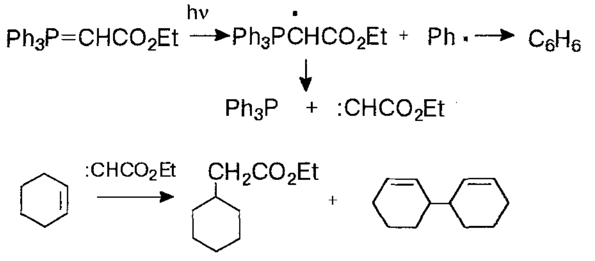
[a] Ph_2PO_2H was obtained in 18% yield

Depending on the wavelength of the exciting radiation, irradiation of triphenyl-phosphonium diphenylmethylide generates triphenylphosphine. Triphenylphosphonium diphenylmethylide after irradiation in cyclohexene produces diphenylmethane, 1,1,2,2-tetraphenylethane, and 1,1′-bicyclohexene-2 and triphenylphosphine (Scheme 2.37)[293].



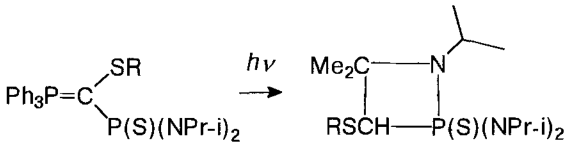
Scheme 2.37

Photolysis of triphenylphosphonium carboethoxymethylide in cyclohexene generates the ethoxycarbonylcarbene resulting in a mixture of products, including benzene, in quantitative yield—as shown in Scheme 2.38:



Scheme 2.38

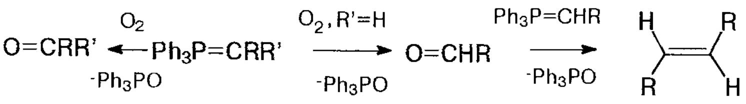
A new cleavage reaction was recently reported in which irradiation of a P-ylide affords nearly quantitatively thiaazaphosphetane and triphenylphosphine. Insertion of the corresponding carbene intermediate into the methine CH bond is probable (Eq. 2.149)[295]:



(2.149)

2.3.2.3 Oxidation—Industrial Synthesis of β-Carotene

The oxidation of phosphorus ylides is one of the most important preparative reactions in phosphorus ylide chemistry. Phosphorus ylides are generally susceptible to oxidative cleavage producing carbonyl compounds or alkenes and phosphine oxides. Monosubstituted phosphorus ylides are usually oxidized to alkenes Oxidation of disubstituted ylides provides ketones. Phosphonium ylides can be oxidized by various oxidants, *e.g.* oxygen[296,297], ozone[298], ozone–triphenylphosphite adduct[299], periodate[300,301], potassium permanganate[302], hydrogen peroxide[303], peracids[304,305], selenium dioxide[148], oxone[312-315], etc. (Table 2.13). The oxidation of phosphorus ylides with molecular oxygen results in cleavage of the P=C bonds to provide the corresponding ketones or alkenes (Eq. 2.150).



(2.150)

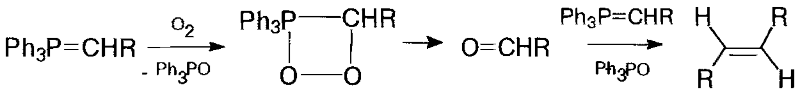
Table 2.13 Oxidation of phosphorus ylides

Oxidizer	Conditions	Ref.
Oxygen	hv, r.t., CH_2Cl_2, C_6H_6	217,296,297,309
Ozone	-70°C, CH_2Cl_2	298,310-312
$(PhO)_3PO_3$	-78°C- -35°C	299,318,319,321,324
Dimethyldioxirane	-78- +25°C, CH_2Cl_2/acetone	314
Peracids	r.t., CH_2Cl_2	304,305,316,317
Potassium permanganate	r.t., H_2O, benzene	302
Hydrogen peroxide	H_2O, 0→20°C, -15 -30°C	300,303,
H_2SeO_3	reflux in dioxane, 2.5- 7 h	128
N-Camphorsulfonyloxaziridine	THF, -78- +25°C	306,307
$NaIO_4$	reflux in water, 1 h; reflux in ethanol, 2-3 h	301
Na_2O_2	DMF, 15- +20°C	
t-butylhydroperoxide	heptane, toluene, -10-20°C	303
Oxone	25-60°C, CH_2Cl_2, C_6H_6/H_2O	312-315

Reaction of C-monosubstituted ylides with the one-half equivalent of oxygen affords, initially, aldehydes which then react readily with excess starting ylide to for symmetrical alkenes. The oxidation of C,C-disubstituted phosphorus ylides leads to the formation of ketones which react with starting ylide relatively slowly, enabling autooxidation resulting in complete conversion of ylide to ketone[248,299,308].

The reactivity of phosphorus ylides with molecular oxygen depends on their nucleophilicity. Non-stabilized ylides are readily oxidized by oxygen whereas the reaction of stabilized ylides with oxygen proceeds very slowly. More active oxidants must be used for oxidation of stabilized ylides. Because non-stabilized phosphorus ylides usually readily undergo autooxidation, the preparation of non-stabilized phosphorus ylides must be performed under inert gas. Oxygen should be excluded from the environment.

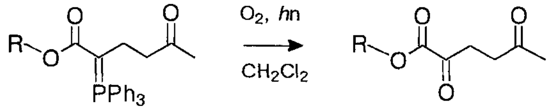
The autooxidation of ylides probably proceeds via the formation of four-membered cyclic intermediates, similar to those formed in the Wittig reaction[309]. Akasaka and Sago[309] investigated the oxidation of triphenylphosphonium 1-methyltrimethylsilylbenzylide with singlet oxygen at low temperature and found that the reaction really does proceed via a four-membered cyclic phosphadioxetane (R = $SiMe_3$) containing the pentacoordinate phosphorus atom (Eq. 2.151). The initial ylide-oxygen adduct was detected by ^{31}P NMR spectroscopy.



(2.151)

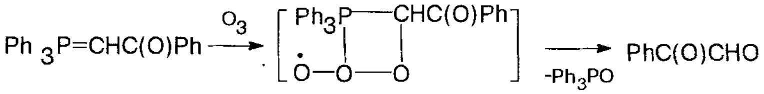
The reaction of triphenylphosphonium methoxycarbonylmethylide with singlet oxygen gives *α*-ketocarboxylic acids. The general procedure consists in placing the ylide in a solvent such as chloroform, benzene, or methanol, adding rose Bengal as a sensitizer, and then irradiating with light from a 500-W tungsten filament lamp while oxygen is passed through the solution. After a few minutes the solution is filtered to remove triphenylphosphine oxide and the ketocarboxylic ester is recovered in yields of 94–100%. Photooxygenation of triphenylphosphonium methoxycarbonylbenzylide for a few minutes at 10°C results in quantitative yield of methyl phenylglyoxylate (Eq. 2.152, R = Me, Et, Ph)[297]. Bestmann and coworkers described the photochemical oxidation of triphenylphosphonium 1-carboalkoxy-4-oxopentylides with singlet oxygen, furnishing bright yellow triones (Eq. 2.153, R = MeO_2C, EtO_2C)[217].

$$Ph_3P{=}CRCO_2Me + O_2 \longrightarrow RCOCO_2Me + Ph_3PO \qquad (2.152)$$



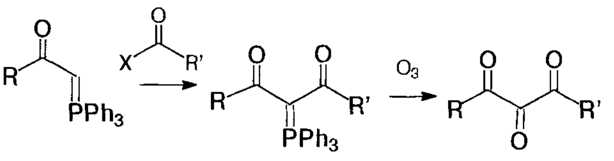
(2.153)

Stabilized phosphorus ylides readily undergo oxidation with ozone. For instance, triphenylphosphonium phenacylide is inert to oxygen but reacts with ozone at -70°C in dichloromethane forming phenylglyoxal and triphenylphosphine oxide (Eq. 2.154)[298]:



(2.154)

Hon Jung Son and coworkers showed that the ozonolysis of stabilized phosphorus ylides affords esters of *trans-α,β*-unsaturated acids or ketones in high yields and high stereoselectivity[310]. Wasserman and coworkers[311,312] developed the method for the preparation of vicinal 1,2,3-tricarbonyl compounds useful in natural product synthesis, via oxidation of ketocarboxyl ylides with ozone and the singlet oxygen (Eq. 2.155):



(2.155)

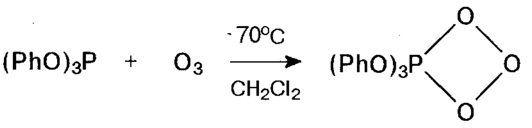
The oxidation of stabilized phosphorus ylides by *peracids* results in the formation of phosphine oxides and olefins which are products of the coupling of the carbanion groups of the ylide (Eq. 2.156)[316,317]:

$$2Ph_3P{=}CHC(O)Ph \xrightarrow[-Ph_3PO]{MeCO_3H} PhC(O)CH{=}CHC(O)Ph \qquad (2.156)$$

Reaction of triphenylphosphonium benzylide with peracetic acid (Eq. 2.156)[316]

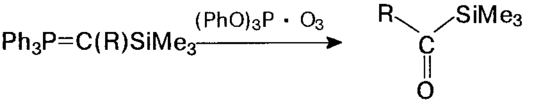
A solution of percaprylic acid (2.56 g, 0.016 mol) in dichloromethane (26 mL) was added to a stirred solution of triphenylphosphonium *p*-nitrobenzoylmethylide (6.5 g, 0.015 mol) in dichloromethane (75 mL) at –30°C. The solution was stirred for 15 h and then concentrated in vacuo until crystallization occurred. Filtration afforded 1.14 g (46%) of *p,p*-dinitrobenzoylethylide, mp 203–209°C, which was recrystallized from dichloromethane, mp 208–211°C.

Good results were obtained from the oxidation of stable ylides with 50% *hydrogen peroxide*. By this method, in particular, symmetrical carotenoids were obtained. One of the best oxidants of phosphorus ylides is *the adduct of triphenylphosphite with ozone*[299]. This oxidant does not contain the protons, can be used at low temperature, reacts with both non-stabilized and stabilized ylides, is aprotic on nature, can be easily dispensed, and furnishes high yields of the final products. This reagent is readily prepared by treatment of triphenylphosphite with ozone at –78°C (Eq. 2.157)[318]. Unfortunately this reagent is not stable—above +35°C the adduct decomposes to triphenylphosphate and oxygen. However the adduct is very active and reacts with phosphorus ylides at low temperatures to provide ketones in 73–81% yields and olefins in 48–87% yields[299]:



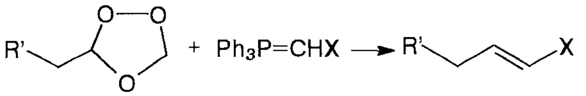
(2.157)

Oxidation of C-silyl-substituted phosphonium ylides with the $(PhO)_3P{\cdot}O_3$ results in acylsilanes, including bis(trimethylsilyl)ketone (Eq. 2.158)[319,321]:



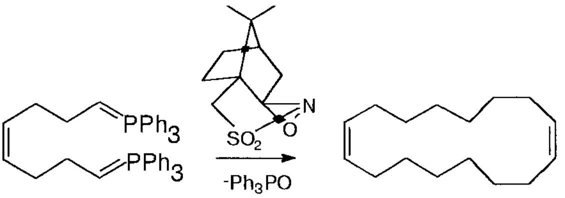
$$Ph_3P{=}C(R)SiMe_3 \xrightarrow{(PhO)_3P\,\cdot\,O_3} R(SiMe_3)C{=}O \qquad (2.158)$$

Ozonides obtained from monosubstituted alkenes are reported to react with stabilized ylides to give the corresponding alkenes in good to excellent yield (Eq. 2.159)[320]. Wasserman and Baldino proposed dimethyldioxirane (Me_2CO_2) for selective oxidation of phosphorus ylides under mild conditions (CH_2Cl_2–acetone, –78→25°C) in very high yields (70–100%)[314]. Vicinal tricarbonyls are easily prepared by selective oxidation of phosphorus ylides with Me_2CO_2. No special precautions, for example exclusion of water or atmospheric oxygen, are required for this reaction.



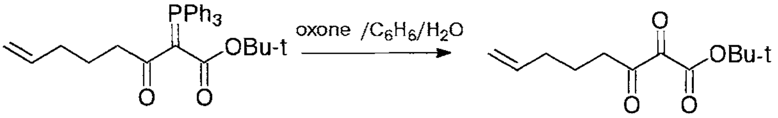
(2.159)

Interesting oxidants of phosphorus ylides are *N-sulfonyloxaziridines*, which react with phosphorus ylides similarly to the adducts of triphenylphosphite with ozone. *N*-Sulfonyloxaziridines give higher yields of the reaction products and are more suitable than the ozone-triphenylphosphite adduct. They furnish ketones in yields of approximately 100%, and olefins in yields of 60–100% (Eq. 2.160)[306,307]:The oxidation of acylylides with *N*-sulfonyloxaziridines produces 1,2-diketones and the oxidation of diylides furnishes unsaturated macrocycles[307].



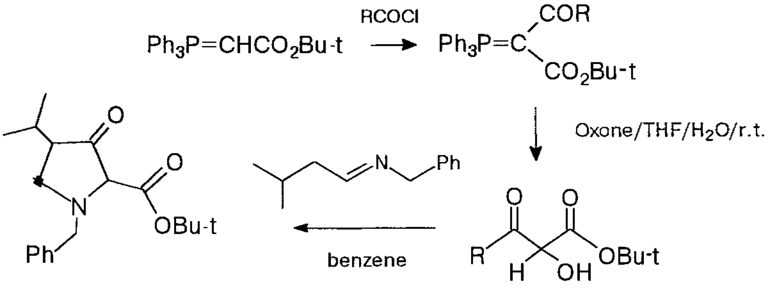
(2.160)

Excellent yields were obtained with *potassium peroxymonosulfate* (commercially available *oxone* = $2KHSO_5.KHSO_4.K_2SO_4$)-induced cleavage of the ylide bond in substituted ylides[313]. This reagent cleaves the carbon–phosphorus double bond under mild conditions. It is possible to achieve oxidative cleavage of the C=P bond in a two-phase system (benzene–H_2O) (Eq. 2.161):



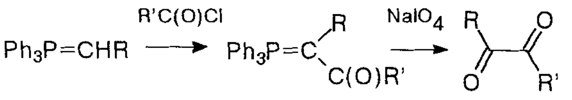
(2.161)

For example, acylation of an ester-ylide with a variety of acyl halides produced α,α–diacylides which upon ozonolysis, afforded vicinal tricarbonyl compounds[312]. Careful oxidation of ylides gives the hydrates of 1,2,3-vicinal tricarbonyl compounds. These react with Schiff bases to yield the pyrrolidine carboxylate (Scheme 2.39)[314,315]. Similarly the C_1–C_{15} α,β-diketoamide subunit of the immunosuppressant FK 506 has been prepared by a similar acylation and ozonolysis of the appropriate ylide[311]:



Scheme 2.39

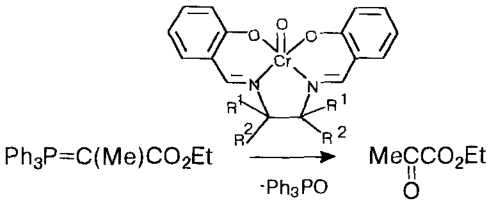
Sodium periodite was reported by Bestmann[300,301] to be one of the most effective oxidants of P-ylides; it converts C-acyl-substituted ylides into 1,2-diketones in yields of 33–100% (Eq. 2.162):The oxidation of phosphorus ylides to alkenes proceeds smoothly with the exchange of the anion of the phosphonium salt with the periodite anion. The action of bases on such salts provides mainly *Z* configuration alkenes in high yields (Eq. 2.163):



(2.162)

$$2[\mathrm{Ph_3\overset{+}{P}CH_2R}]\mathrm{X}^- \xrightarrow{\mathrm{NaIO_4}} 2[\mathrm{Ph_3\overset{+}{P}CH_2R}]\mathrm{IO_4}^- \xrightarrow[-\mathrm{Ph_3PO}]{\mathrm{B}} \xrightarrow{\mathrm{RCHO}} \mathrm{RCH{=}CHR} \qquad (2.163)$$

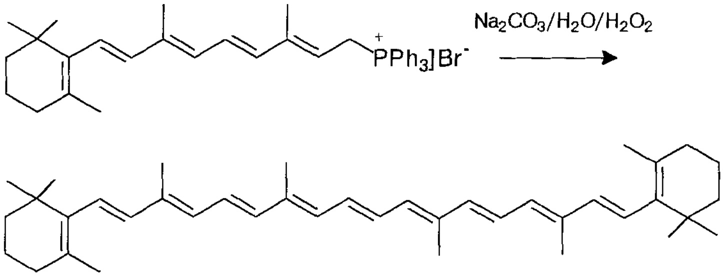
Oxochromium(V) complexes were recently proposed for the oxidation of phosphorus ylides (Eq. 2.164)[322,323]:



(2.164)

Examples of Application in Organic Synthesis

Hydroxide oxidative olefination has been applied for the industrial synthesis of symmetrical carotenoids. The starting phosphonium salts were synthesized from vitamin A and triphenylphosphane.HBr and deprotonated by sodium carbonate to give the corresponding ylide, which was oxidized to afford crystalline β–carotene in very good yield. The oxidation, by molecular oxygen or by the triphenylphosphite–ozone adduct, of the ylide formed by dehydrohalogenation of the phosphonium salt results in the formation of β–carotene. Use of hydrogen peroxide in this manner enabled workers at BASF AG to create a simple process for the synthesis of β–carotene which was used on an industrial scale[324]. The oxidation with hydroperoxide has the advantage that it can be performed in aqueous medium (Eq. 2.165):

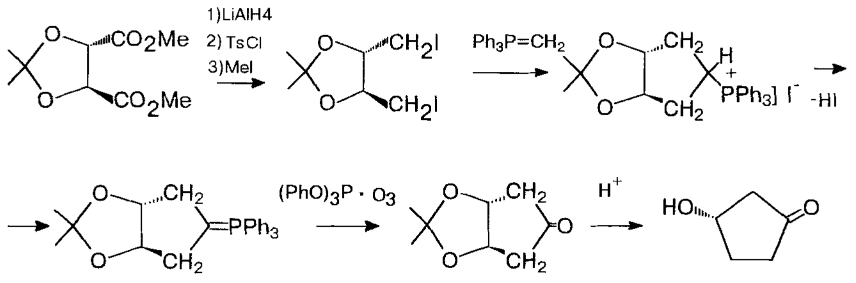


(2.165)

***Synthesis of β–carotene** (Eq. 2.165)*[303]

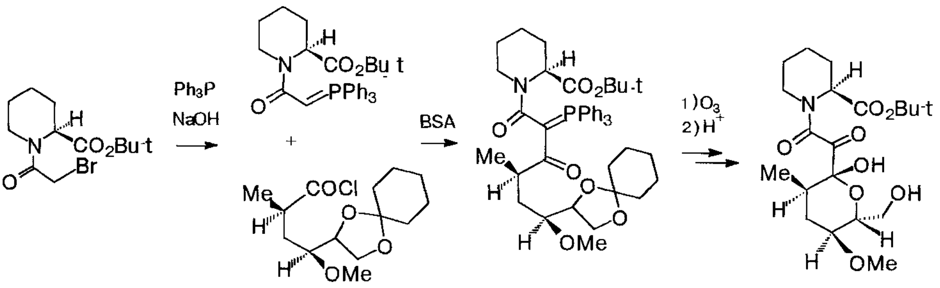
A solution of the phosphonium salts (3.14 g, 0.5 mol) in 2.5 l of waters was placed into a flask and 72.5 ml of 30% hydrogen peroxide was added. Then a solution of sodium carbonate (75 g, 0,8 mol) in 250 ml of waters was added dropwise for a 1 h. The reaction mixture was stirred overnight at the room temperature. Then the mixture of β–carotene and triphenylphosphine oxide was filtered off and washed with hot water at 70° C. The precipitate was suspended in 4.5 l of waters and refluxed for 20 h under nitrogen. Then the *β*-carotene was against filtered off and washed with 1.5 l of warm methanol to remove the triphenylphosphine oxide. Filtration and drying furnished 107 g (80%) of *β*-carotene, mp 181-183°C

The oxidation of phosphorus ylides is the key step in the preparation of hydroxycyclopentenone derivatives, valuable building blocks for the synthesis of cyclopentanoid natural products, including prostaglandins. Thus, the bis-iodide obtained from dimethyl ester of *R*,*R*-tartaric acid undergoes a ring-closure reaction with 2 mol triphenylphosphonium methylide to form the cyclic phosphonium salt, dehydrohalogenation of which provides the phosphorus ylide. Subsequent Wittig reaction with aldehydes leads to the formation of the alkene, which was reduced to the optically active substituted dihydroxycyclopentane derivative. Oxidation of the ylide with the triphenylphosphite–ozone complex leads to the ketone, which was hydrolyzed to give the hydroxycyclopentenone (Scheme 2.40)[325]:



Scheme 2.40

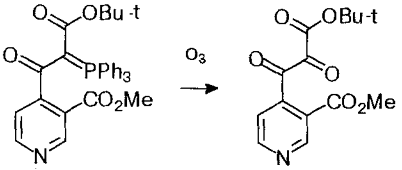
Many highly bioactive compounds (macrocyclic lactone FK-506, the potent immunosuppresant, rapamycin, 29-dimethoxyrapamycin, and others) contain a 1,2,3-tricarbonyl group. Particular attention has, therefore, been devoted to the formation of vicinal 1,2,3-tricarbonyl systems. Wasserman and coworkers proposed the synthesis of the C_1–C_{15} *α*,*β*-diketoamide subunit of FK-506 via the oxidation of P-ylides (Scheme 2.41)[311].



Scheme 2.41

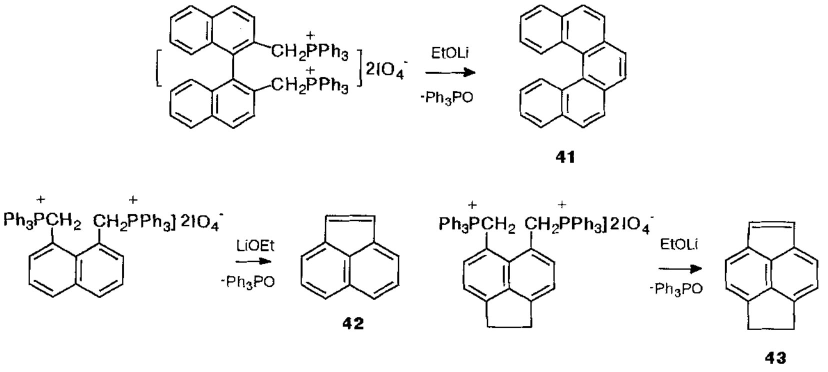
The synthesis began with the *tert*-butyl ester of (–)-pipecolinic acid, which was coupled with α–bromoacetic acid to give the bromoacetyl derivative, converted then into an ylide. Oxidative cleavage of the ylide with either ozone or singlet oxygen yielded the α,β–diketoamide after removal of triphenylphosphine oxide by chromatography. The tricarbonyl was then converted in dilute acidic methanol to the hemiketal, subunit of FK-506.[311].

Vicinal tricarbonyl structures useful as polyelectrophiles in the synthesis of vincamine-related alkaloids have been prepared by oxidation of β,β-dicarbonyl ylides with ozone and singlet oxygen (Eq. 2.166)[326,327]:



(2.166)

Oxidation of phosphorus ylides via exchange of the anion of phosphonium salts on the periodite anion has been used for intramolecular cyclizations. For instance, the treatment of the bis(phosphonium)periodite with lithium ethylate at –50°C affords *R*-pentagelicene. The yields of cyclic compounds **41**–**43** are 75–85% (Scheme 2.42)[308]:



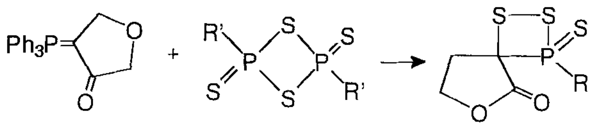
Scheme 2.42

Symmetric cis scipped polyenmic hydrocarbons have been prepared using stereoselective oxidative dimerization of P-ylides.[309b]

2.3.2.4 Reactions with Elemental Sulfur and Selenium

Phosphorus ylides react with the sulfur (and also with selenium and tellurium) with formation of thiocarbonyl (seleno-, tellurocarbonyl) compounds and phosphine sulfides (selenides, tellurides).

The initial reaction of phosphorus ylides with the sulfur is, probably, attack of the ylidic carbon atom on the sulfur atom, resulting in the formation of an intermediate betaine which is converted into an unstable four-membered cyclic dithiaphosphetane. The latter decomposes readily to afford the thiocarbonyl compound and phosphine sulfide[329]. The dithiaphosphetane intermediates were isolated by Yousif[328] by addition reaction of the P-ylide with 1,3,2,4-dithiadiphosphetane-2,4-disulfide in dichloromethane at room temperature (Eq. 2.167).



R=4-MeOC6H4

(2.167)

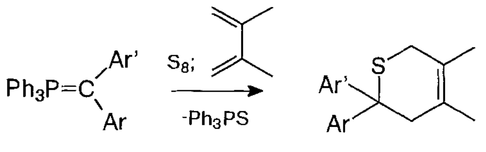
Reaction of the triarylphosphonium diarylmethylides with the sulfur furnishes thiobenzophenones and triphenylphosphine sulfide in yields of 51–85%[329–331] Occasionally, however, polysulfides are formed (Eq. 2.168):

$$Ph_3P{=}CPh_2 \xrightarrow{S_8} Ph_3P{=}S + Ph_2C{=}S \qquad (2.168)$$

Thiobenzophenone (Eq. 2.168)[330]

A mixture of triphenylphosphonium diphenylmethylide (23.4 g, 0.055 mol) and sulfur (3.5 g) in benzene (200 mL) was heated under reflux for 1 h under nitrogen. The solvent was then removed and the residue was distilled under vacuum, bp 104–107°C (50 Pa). The blue distillate solidifies in a short time, mp 49–51°C. Yield: 9.3 g (85%). The crystallization of the residue in the flask from ethanol affords the triphenylphosphine sulfide, mp 156–158°C.

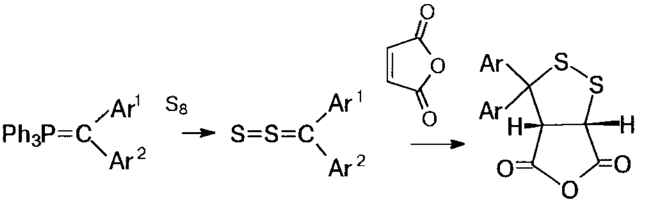
The thiobenzophenone formed readily undergoes cycloaddition reactions with unsaturated compounds. Thus the reaction of triphenylphosphonium diphenylmethylide with elemental sulfur in the presence of dimethyl acetylenedicarboxylate or dienes results in the [4+2]-cycloaddition products (Eq. 2.169)[332–336]:



(2.169)

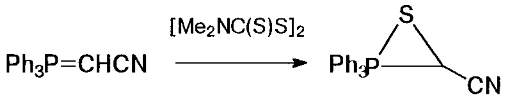
Okuma and coworkers reported the reaction of the triphenylphosphonium diarylmethylides with excess sulfur which led to the formation of very active thiosulfines (Eq. 2.170). The latter compounds were trapped with maleic anhydride with the formation of 1,2-dithiolanes in very good yields[332,337]:

Triphenylphosphonium carbomethoxymethylide reacts with sulfur to furnish dimethyl maleate and dimethyl fumarate in a 1:4 ratio. It was shown that the thio-Wittig reaction proceeds via a thiophosphetane intermediate[338]. The reaction of C-monosubstituted ylides with sulfur affords olefins and phosphine sulfide. For instance, as was shown by Meyer[339], the reaction of the triphenylphosphonium arylides with elemental sulfur in toluene at 110°C furnishes 1,2-diarylethylenes in yields of 71–93%.



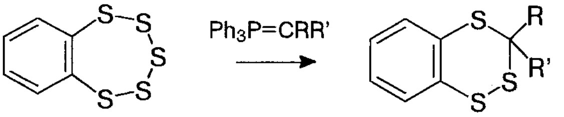
(2.170)

Reaction of the triphenylphosphonium propylide with sulfur, however, furnishes the 3-hexene in yield of 28%[339]. The reaction of stabilized P-ylides with tetramethylthiuram disulfide furnishes cyclic adducts (Eq. 2.171):



(2.171)

1,2,3-Benzotrithins have been synthesized in moderate to good yields by the reaction of triphenylphosphonium alkylylides with benzopentathiepin (Eq. 2.172) [339a]:



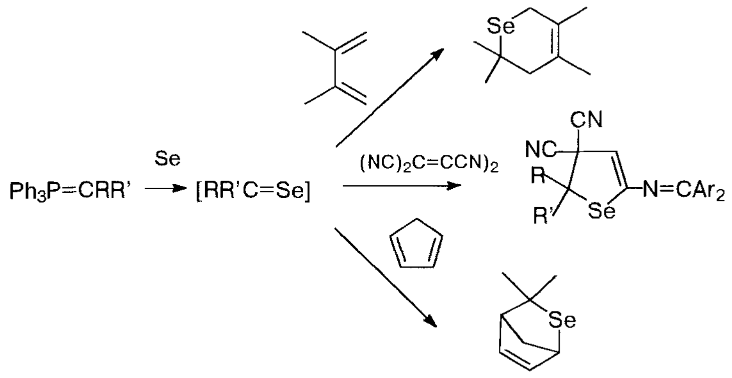
(2.172)

The reaction between elemental selenium and C-monosubstituted phosphorus ylides results in the cleavage of the P=C bond and the formation of triphenylphosphine and olefins, the latter formed by dimerization of the carbonic fragment of the ylide (Eq. 2.173).[342] Phosphine selenide catalyzes the conversion of phosphorus ylides into olefins[340–342]:

$$Ph_3P=CHR + Se \longrightarrow Ph_3P + RCH=CHR \qquad (2.173)$$

Thus, heating of triphenylphosphonium benzylide (58 mmol) under reflux in toluene (100 mL) with selenium (5.8 mmol) for 6 h affords stilbene in 64% yield and triphenylphosphine in 70% yield. This procedure was used to obtain 2-butene (53%), 3-hexene (50%), 4-octene (50%), and 5-decene (63%) as mixtures of the *Z* and *E* isomers (~85:15). The reaction proceeds via the formation of selenocarbonyl compounds, which in view of their instability were trapped with 2,3-dimethylbutadiene or cyclopentadiene according to the Diels–Alder reaction with the formation of selenium-containing heterocyclic compounds (Scheme 2.43)[343].

The reaction of selenobenzophenones with tetracyanoethylene furnishs cyclo-adducts, sharply different from the results obtained with thiobenzophenones[344].



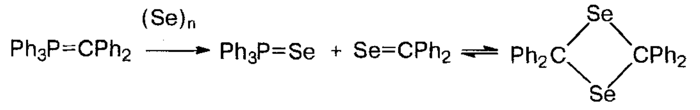
Scheme 2.43

Triphenylphosphonium diarylmethylides react with elemental selenium to form selenocarbonyl compounds with monomeric or dimeric structures (Eq. 2.174)[343–335].

$$Ph_3P{=}CAr_2 \xrightarrow{Se} Se{=}CAr_2 \qquad (2.174)$$

Ar= Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$

Triphenylphosphonium diphenylmethylide reacts with elemental selenium in toluene at 85°C to give the selenobenzophenone[345], as a solution of the monomer which enters into [2+4]-cycloaddition reactions with dienes. On removal of the solvent selenobenzophenone was converted into the cyclic dimer which was isolated as crystalline compound in 76% yield (Eq. 2.176)[345,346]. Monomeric 4,4′-dimethoxy- and 4,4′-dimethylselenobenzophenones were isolated as stable green crystals and theirs structures were proved by X-ray crystallography[344]:



(2.175)

4,4′- Dimethoxyselenobenzophenone (Eq. 2.175)[345]

Butyllithium (2.2 mmol) was added at room temperature to a degassed solution of bis(4-methoxyphenyl)methyltriphenyl-phosphonium tetrafluoroboramide (1.15g, 2.0 mmol) in benzene (40 mL). The mixture was stirred for 30 min, and then selenium powder (0.47 g, 6.0 mmol) was added in portions and the mixture was heated under reflux for 30 min. The resulting suspension was filtered to give a green solution which was evaporated to give a green solid. This solid was chromatographed over silica gel with pentane-dichloromethane, 4:1, as eluent to give crude desired compound. Yield 0.354 g (58%). Green crystals, which were recrystallized from pentane to afford green needles, mp 98–99°C.

2.3.2.5 Reduction

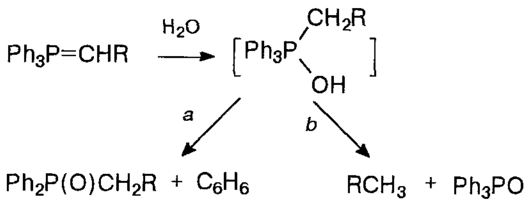
Reduction of phosphorus ylides, and oxidation and hydrolysis, proceeds with cleavage of the carbanion–phosphorus bond. Studies of the reduction of phosphorus ylides have shown that every hydrocarbon group can be removed from the phosphorus. The first group to be cleaved from the phosphorus as a hydrocarbon is that group which forms the most stable carbanion. Thus the reduction of benzyl-stabilized triphenylphosphonium ylides with lithium aluminum hydride results in the elimination of one of alkyl groups from the phosphorus atom to afford triphenylphosphine, whereas triphenyl-phosphonium alkylides furnish alkyldiphenylphosphines under these conditions (Eq. 2.176)[346a]. The reduction of ketoylides with zinc in acetic acid proceeds with cleavage of then P=C bond to afford triphenylphosphine and ketone (Eq. 2.177)[31]:

$$Ph_2PAlk + C_6H_6 \xleftarrow{R=Alk} Ph_3P{=}CHR + LiAlH_4 \xrightarrow{R=Ph} Ph_3P + RCH_3 \tag{2.176}$$

$$Ph_3P{=}C(R)COR \xrightarrow{Zn} Ph_3P + RCH_2C(O)R' \tag{2.177}$$

2.3.2.6 Hydrolysis of Ylides

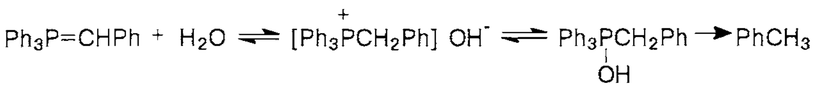
Hydrolysis of phosphorus ylides results in cleavage of the carbon–phosphorus multiple bond. The ylidic carbon atom is converted to a methyl or methylene group, producing hydrocarbons, whereas the phosphorus becomes a P=O group. Susceptibility to hydrolysis depends on the structures and the reactivity of the ylide. Non-stabilized ylides, for example triphenylphosphonium alkylides, react immediately with moisture. Ylides stabilized with electron-accepting groups are hydrolytically stable and can be obtained from phosphonium salts in aqueous solution. The hydrolysis of stabilized ylides is achieved by lengthy reflux in water–alcohol solutions. The hydrolysis of phosphorus ylides probably proceeds via the hydroxyphosphorane which readily eliminates one of the groups connected to the phosphorus to afford a phosphine oxide and the corresponding hydrocarbon: hydrolysis of a series of C-substituted triphenylphosphonium ylides showed that the group forming the most stable carbanion is the most easily removed from phosphorus: benzyl > phenyl > alkyl (Scheme 2. 44)[347].



a - H, Me, OMe; *b*: R=Ph, Ms, SAlk, Cl, Br

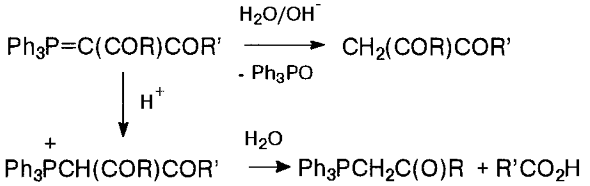
Scheme 2. 44

Substituents destabilizing the ylidic carbanion, for instance alkoxy groups, favor the elimination of benzene during hydrolysis. At the same time electron-accepting groups stabilizing the ylidic carbanion, such as thioalkyl groups or halogen atoms, favor hydrolytic cleavage of the ylides with the formation of triphenylphosphine oxide and substituted methane[348,349]. Kinetic studies of the hydrolysis of phosphorus ylides showed that the slow step of the reaction is the cleavage of the P=C group[347]. Reducing the polarity of the solvent increases the concentration of hydroxyphosphorane in equilibrium with the phosphonium hydroxide (Eq. 2.178)[350–352]:



$$Ph_3P{=}CHPh + H_2O \rightleftharpoons [Ph_3\overset{+}{P}CH_2Ph]\,OH^- \rightleftharpoons Ph_3\underset{\displaystyle OH}{\underset{|}{P}}CH_2Ph \longrightarrow PhCH_3 \qquad (2.178)$$

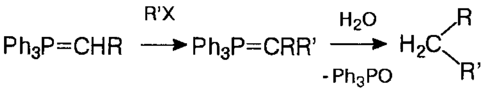
Hydrolysis of the phosphorus ylide can be performed in alkaline, acidic or neutral media and depending on the medium the hydrolysis can proceed in different directions (Scheme 2. 45). In acid media α,α–diacetylmethylides eliminate an acetyl group with the formation of acetylmethyltriphenylphosphonium salts[348] whereas under neutral or basic conditions hydrolysis of acetylmethylides proceeds with cleavage of the P=C bond producing a triphenylphosphine oxide and a hydrocarbon[163]:



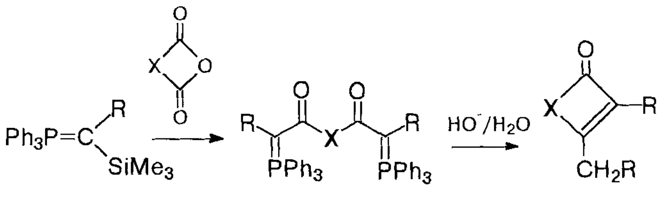
Scheme 2. 45

2.3.2.7 Applications in Organic Synthesis

The hydrolysis of phosphorus ylides has preparative application because it is one of many reactions which lead to cleavage of the P=C bond. The hydrolysis of phosphorus ylides has been applied as the final step of many synthetic sequences after modification of a starting ylide by acylation, alkylation or arylation (Eq. 2.179): For example, alkaline hydrolysis of bis(1-acylalkylidenetriphenylphosphoranes) prepared from the corresponding acid anhydride are useful methods for the synthesis of a,β–unsaturated cyclohexenones (Eq. 2.180)[55]:

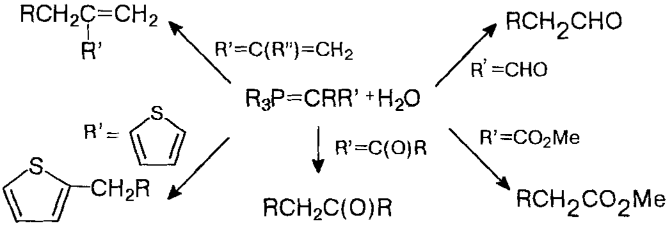


$$Ph_3P{=}CHR \xrightarrow{R'X} Ph_3P{=}CRR' \xrightarrow[-Ph_3PO]{H_2O} H_2C\begin{smallmatrix}R\\R'\end{smallmatrix} \qquad (2.179)$$



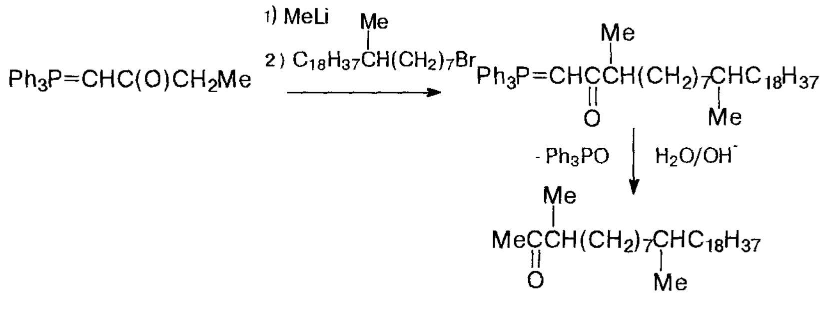
(2.180)

The hydrolysis of phosphorus ylides enables the preparation of different compounds: aldehydes[354], ketones[360,376], acids[164], heterocyclic compounds[355], hydrocarbons[356], and cyclic hydrocarbons[357], etc. (Scheme 2. 46).



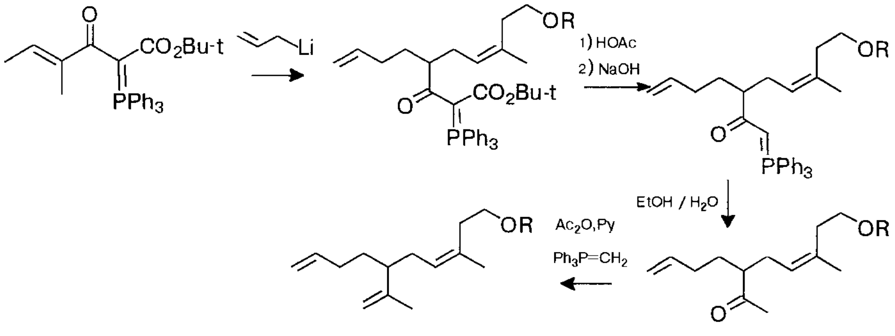
Scheme 2. 46

Insect sex pheromones of the German cockroach were synthesized by alkylation of the triphenylphosphonium 2-oxobutylide with an alkyl bromide and subsequent alkali hydrolysis of C-alkylated ylide formed (Scheme 2. 47)[353]:



Scheme 2. 47

Anions generated by addition of nucleophiles to α,β-unsaturated acylylides were converted under acidic conditions to substituted ylides, which were hydrolyzed to methyl ketones. The utility of these unsaturated acylylides as methylvinylketone equivalents in conjugate addition-alkylation reactions is demonstrated in the synthesis of the pheromone of the California red scale (Scheme 2. 48)[358,359]:



Scheme 2. 48

2.3.3 Substitution at the Ylidic Carbon Atom

Hydrogen atoms on the ylidic carbon atom are comparatively mobile[360] and can be replaced by various substituents, resulting in the formation of phosphonium salts or new phosphorus ylides. The replacement of the hydrogen atoms on the ylidic carbon atom by other substituents can be performed by two routes:

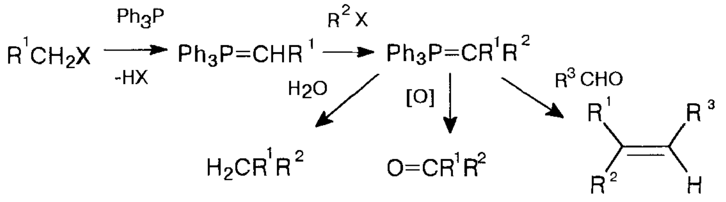
a) substitution of the hydrogen atoms by reaction of the phosphorus ylides with different halogen containing electrophiles; and
b) Michael addition of compounds containing electron-deficient C=C and C≡C multiple bonds to ylides.

2.3.3.1 Reactions with Alkylation Reagents

Phosphorus ylides are active nucleophiles, they react with alkyl halides to afford C-alkylated phosphonium salts or, if the phosphonium salt enters into a transylidation reaction with excess ylide, phosphorus ylides (Eq. 2.181):

$$Ph_3P{=}CHR \xrightarrow{R'X} [Ph_3\overset{+}{P}CHRR']\,X^- \xrightarrow[-HX]{B} Ph_3P{=}CRR' \qquad (2.181)$$

The alkylation of phosphorus ylides is one of the most widely explored and useful reactions in phosphorus ylide chemistry. Alkylation of phosphorus ylides is important synthetical tool for constructing carbon frameworks previously obtained with difficulty. This reaction enables the connection of two different alkyl halide radicals. After the alkylation the phosphonium group of the ylide can be removed by one of the P-ylide cleavage reactions (oxidation, hydrolysis, Wittig reaction) to provide organic compounds bearing an hydrocarbon chain (Scheme 2. 49). The alkylation of phosphorus ylides has been used for the preparation of phosphonium salts, of small, middle and macrocycles, of heterocyclic compounds, of derivatives of unsaturated carbonic acids, and so on.



Scheme 2. 49

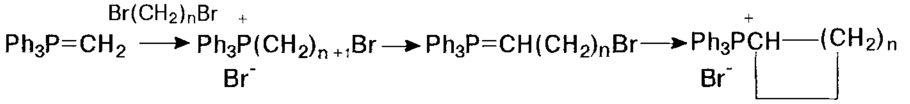
Alkylation of phosphorus ylides enables the preparation of sterically hindered phosphonium salts which are otherwise difficult to prepare. For instance, *tert*-butyltriphenylphosphonium iodide has been synthesized by alkylation of phosphonium ylides (Eq. 2.182)[361]. The alkylation of tri(*tert*-butyl)phosphonium ethylide with methyl bromide furnishes tetra(*tert*-butyl)-phosphonium iodide (Eq. 2.183)[362]: The tetra (isopropyl)phosphonium salt was prepared by alkylation of tri(isopropyl)phosphonium ethylide with methyl iodide. Deprotonation of tetra(isopropyl)phosphonium iodide with sodium amide furnishes the phosphorus ylide (Eq. 2.184)[363,364]:

$$\mathrm{Ph_3P{=}CMe_2} \xrightarrow{\mathrm{MeI}} [\mathrm{Ph_3\overset{+}{P}CMe_3}]\,\mathrm{I^-} \qquad (2.182)$$

$$\text{t-}\mathrm{Bu_3P{=}CHMe} \xrightarrow{\mathrm{MeBr}} [\text{t-}\mathrm{Bu_3\overset{+}{P}CHMe_2}]\mathrm{Br^-} \longrightarrow \text{t-}\mathrm{Bu_3P{=}CMe_2} \xrightarrow{\mathrm{MeI}} [\text{t-}\mathrm{Bu_4\overset{+}{P}}]\mathrm{I^-} \qquad (2.183)$$

$$\text{i-}\mathrm{Pr_3P{=}CHMe} \xrightarrow{\mathrm{MeI}} [\text{i-}\mathrm{Pr}\ _4]\mathrm{I^-} \xrightarrow{\mathrm{NaNH_2}} \text{i-}\mathrm{Pr_3P{=}CMe_2} \qquad (2.184)$$

The intramolecular alkylation of phosphorus ylides has been extensively used for preparation of different cyclic systems (Eq. 2.185):



(2.185)

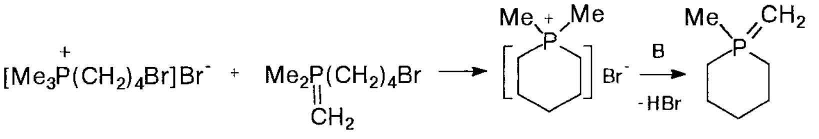
Bestmann and coworkers used this root to obtain phosphorus ylides containing various rings on the ylidic carbon atom[365]. The preparative accessibility of this reaction is demonstrated by next synthesis.

Cyclohexyltriphenylphosphonium bromide[366]

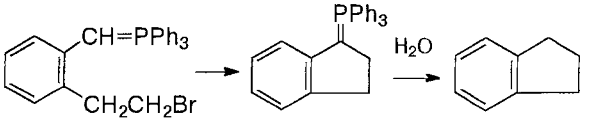
A solution of 1,5-dibromopentane (6.9 g, 30 mmol) in THF (30 mL) was added dropwise to a solution of triphenylphosphonium methylide (60 mmol) in tetrahydrofuran at 50–60°C. The reaction mixture was left for 7 h, then removed by filtration. The solvent was evaporation and the residue recrystallized from water. Yield 11.3 g (88%), mp 267–269°C.

Intramolecular alkylation of phosphorus ylides bearing ω-bromoalkyl substituents furnishes cyclic compounds with rings varying in size from three to seven carbons (Eq.

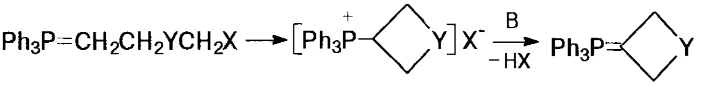
2.186–188)[357,367–369]. Dehydrobromination of phosphonium salts with the blue solution of potassium in hexametapol is followed by intramolecular alkylation to result in an exocyclic five-membered ylide which was hydrolyzed to indan[370].



(2.186)

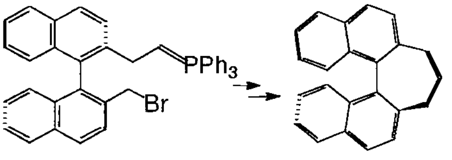


(2.187)



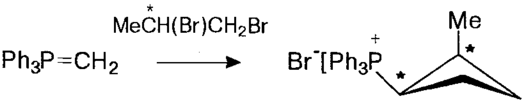
(2.188)

Alkylation of phosphorus ylides with optically active alkyl halides has been used for the preparation of chiral cyclic compounds, for example the synthesis of optically active cyclic 3-*H*-cyclohepta[2,1-*a*;3,3-*a*]dinaphthalene (Eq. 2.189). Another interesting example is the reaction of the triphenylphosphonium methylide with optically active 1,2-dibromopropane, which furnishes an optically active cyclobutylphosphonium salt (Eq. 2.190)[371,372]:



(S)

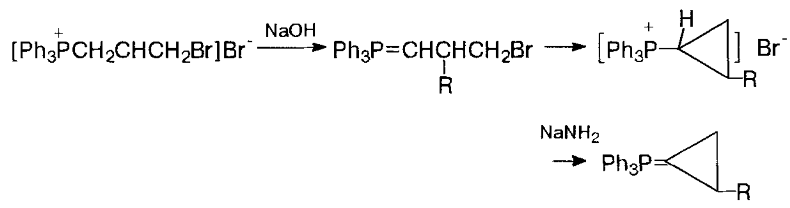
(2.189)



(2.190)

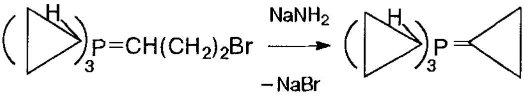
Intramolecular alkylation of *β*-bromoalkylides leads to the formation of phosphonium salts and ylides bearing cyclopropyl groups. 3-Bromopropyltriphenyl-phosphonium bromide reacts with bases to produce cyclopropyl(triphenyl)phosphonium bromide (Eq. 2.191). The deprotonation of the phosphonium salt furnishes the ylide, which undergoes intramolecular alkylation to furnish the cyclopropylphosphonium salt, which is readily deprotonated by sodium amide to afford the highly reactive triphenylphosphonium cyclopropylide, which undergoes the Wittig reaction with carbonyl compounds (Eq. 2.192)[373,374]. Tricyclopropylphosphonium cyclopropylide was obtained by dehydrochlorination of tricyclopropyl-3-bromopropylphosphonium bromide in liquid ammonia at −78°C (Eq. 2.193)[374]. Shmidbauer[374] found that phosphorus ylides containing an alkyl and a cyclopropyl group on the phosphorus (R =

H, Me) exist as prototropic tautomers (Eq. 2.193). The prototropic equilibrium is shifted towards the ylides containing an acyclic ylidic carbanion.

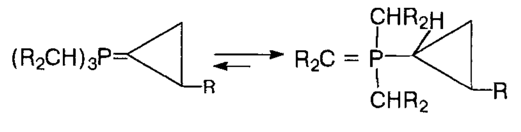


(2.191)

R=H, Me; R^1=Bu, Ph; R^2=H, Me, Et, Ph

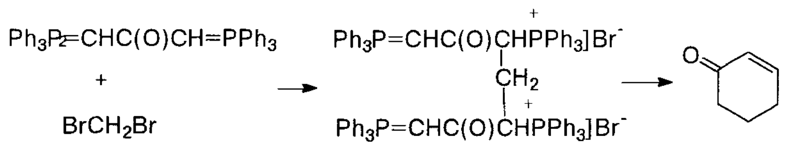


(2.192)



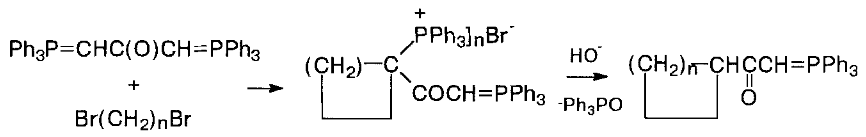
(2.193)

The alkylation of phosphorus ylides can be intermolecular. Alkylation of a bis-ylide with bromomethane affords the bis-ylide phosphonium salt, which was deprotonated and by subsequent hydrolysis transformed into a cyclohexenone (Eq. 2.194)[375,376]:



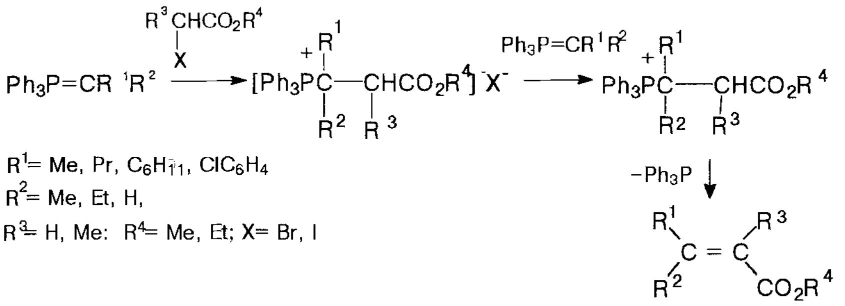
(2.194)

The bis-ylide reacts with dibromoalkanes to afford cycloalkylphosphonium salts, which are hydrolyzed to stable cyclic ylides (Eq. 2.195)[375]:



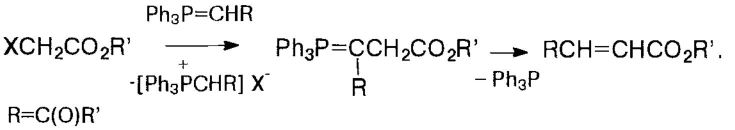
(2.195)

The alkylation of phosphorus ylides sometimes results in phosphonium salts which undergo Hoffmann decomposition. For example phosphonium salts, obtained by reaction of substituted phosphorus ylides with α-halocarboxylic acid esters form phosphonium salts which are readily dehydrohalogenated by excess phosphorylide to form betaines which are converted into β-unsaturated carboxylic acid esters and triphenylphosphine (Scheme 2. 50)[377,378].



Scheme 2. 50

The reaction of acyl-stabilized phosphorus ylides with bromoacetic acid esters affords phosphorus ylides with a mobile hydrogen atom on the β-carbon (Eq. 2.196). These ylides are, therefore, readily deprotonated with excess ylide to result in α,β-unsaturated esters and triphenylphosphine. The final step of the reaction includes intermolecular migration of the hydrogen atom[257,379]:

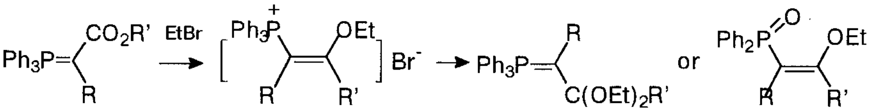


$$XCH_2CO_2R' \xrightarrow[-[Ph_3\overset{+}{P}CHR]X^-]{Ph_3P=CHR} Ph_3P=\underset{R}{C}CH_2CO_2R' \xrightarrow[-Ph_3P]{} RCH=CHCO_2R'. \qquad R=C(O)R' \tag{2.196}$$

Reaction of triphenylphosphonium benzylide with the methyl ether of bromocrotonic acid in 2:1 ratio results in the methyl ester of 5-phenylpentan-2,4-dione acid, triphenylphosphine and phosphonium salts (Eq. 2.197)[380]:

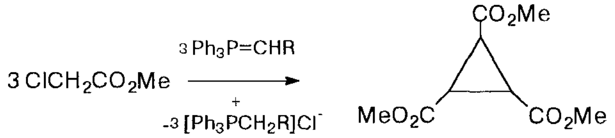
$$\begin{array}{l}2\ Ph_3P=CHPh\\ +\\ BrCH_2CH=CHCO_2Me\end{array} \xrightarrow[{[Ph_3P^+CH_2Ph]Br^-.}]{} PhCH=CHCH=CHCO_2Me + Ph_3P \tag{2.197}$$

The vinylphosphonium salt derived from the ylide reacts with sodium ethoxide to give the phosphine oxide, as was reported by Ruder and Norwood[174], or the phosphorus ylide, as was reported by Bestmann and coworkers[381] (Eq. 2.198):



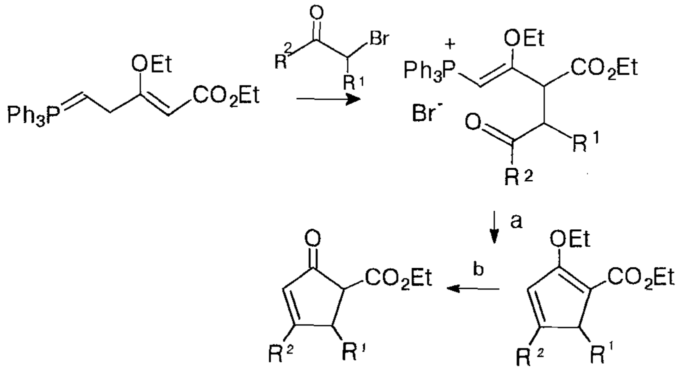
(2.198)

Reaction of triphenylphosphonium alkylides with methyl chloroacetate leads to the formation of tris-1,2,3-methoxycarbonyl-*trans*-cyclopropane (Eq. 2.199)[382]:



(2.199)

A new route to cyclopentadiene and cyclopentenone derivatives in moderate to excellent yields is provided by the reaction of allylic ylides with α-haloketones followed by intramolecular Wittig reaction and acid hydrolysis (Scheme 2. 51)[383a–c]. This reaction sequence has been used in a synthesis of shogaol, the pungent principle of ginger.



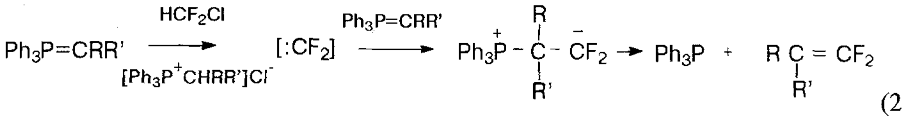
Scheme 2. 51

Barton described an interesting example of the alkylation of phosphorus ylides. The reaction of non-stabilized ylides with chlorodifluoromethane proceeds according to the Wittig reaction with the formation of 1,1-difluoro-1-alkenes. Average yields of difluoroalkenes are 65–100% (Eq. 2.200)[384]:

$$2Ph_3P{=}CRR' \xrightarrow[\overset{+}{[Ph_3PCHRR']Cl^-}]{HCF_2Cl} Ph_3P + F_2C = CRR' \qquad (2.200)$$

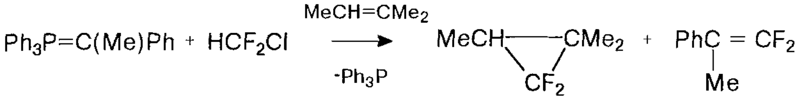
R=H, Me, Ph, c-C_5H_9; R'=Me, Et, Pr, C_6H_{13}, Ph, C_5F_5, OMe, CH=CH_2.

Reaction of an ylide and chlorodifluoromethane proceeds via generation of the difluorocarbene, which is trapped by a nucleophilic ylide to afford a betaine which decomposes to furnish triphenylphosphine and an olefin (Eq. 2.201). Difluorocarbene has been trapped with 2,3-dimethyl-2-butene (Eq. 2.202):



$$Ph_3P{=}CRR' \xrightarrow[{[Ph_3\overset{+}{P}CHRR']Cl^-}]{HCF_2Cl} [:CF_2] \xrightarrow{Ph_3P=CRR'} Ph_3\overset{+}{P}-\underset{R'}{\overset{R}{C}}-\overset{-}{C}F_2 \rightarrow Ph_3P + R\underset{R'}{C} = CF_2$$

(2.201)

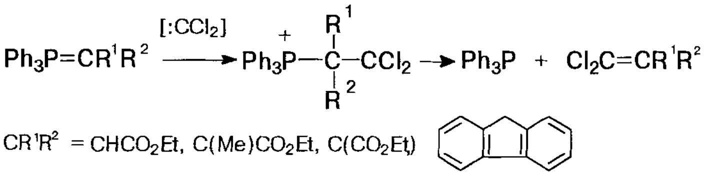


(2.202)

1,1-Difluoro-2,2-diphenylethylene (R = R′ = Ph) (Eq. 2.201)[384]

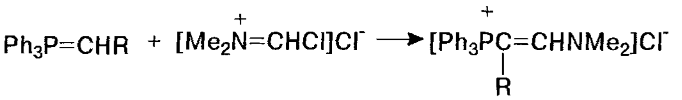
A solution of methyllithium (0,054 mol) in ether was added dropwise to diphenylmethyltriphenylphosphonium bromide (0.054 mol) with stirring and cooling to 0°C. The deep-red solution of the ylide was stirred for 1 h at room temperature and then chlorodifluoromethane (6.92 g, 0.08 mol) was condensed into the reaction solution. After stirring for 72 h at room temperature the reaction mixture was removed by filtration, the mother solution was evaporated under vacuum and pentane was added to the residue. The precipitate of triphenylphosphine was removed by filtration and the pentane was removed in vacuo. The residue was distilled with a 15-cm column. Yield 3.32 g (57%) (GC-determined yield is 62%).

A similar reaction was reported by Oda and coworkers[385] who found that dichlorocarbene generated by decomposition of sodium trichloroacetate reacts with stabilized ylides to afford dichloroolefins. The attack of electrophilic carbene on the ylidic carbon atom gives a betaine which decomposes to triphenylphosphine and olefin (Eq. 2.203):



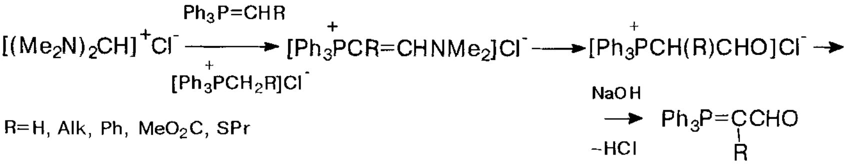
(2.203)

α-Chloroalkylamines react with phosphorus ylides to furnish enaminophosphonium salts (Eq. 2.204)[161,386]:



$$Ph_3P{=}CHR + [Me_2\overset{+}{N}{=}CHCl]Cl^- \longrightarrow [Ph_3\overset{+}{P}\underset{R}{C}{=}CHNMe_2]Cl^- \qquad (2.204)$$

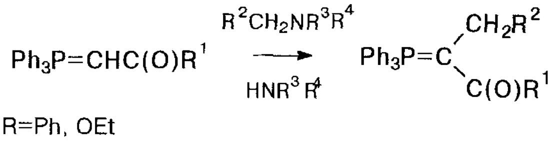
Phosphorus ylides react with tetramethylformamidinium chloride to afford enaminophosphonium chlorides. Treatment of these phosphonium salts with acid and then with base results in formylalkylides (Eq. 2.205)[387].



$$[(Me_2N)_2CH]^+Cl^- \xrightarrow[{[Ph_3\overset{+}{P}CH_2R]Cl^-}]{Ph_3P{=}CHR} [Ph_3\overset{+}{P}CR{=}CHNMe_2]Cl^- \longrightarrow [Ph_3\overset{+}{P}CH(R)CHO]Cl^- \xrightarrow[-HCl]{NaOH} Ph_3P{=}\underset{R}{C}CHO \qquad (2.205)$$

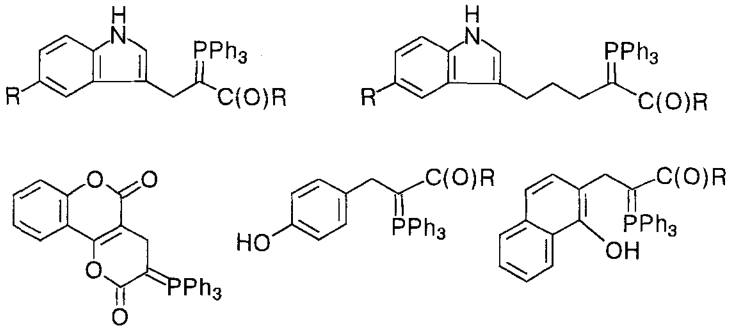
R=H, Alk, Ph, MeO_2C, SPr

The deprotonation of phosphonium salts with sodium amide furnishes the cumuleneylide. Stabilized phosphorus ylides react with Mannich bases to afford C-alkylated ylides in high yields (Eq. 2.206)[388]:



$$\mathrm{Ph_3P{=}CHC(O)R^1} \xrightarrow[\mathrm{HNR^3R^4}]{\mathrm{R^2CH_2NR^3R^4}} \mathrm{Ph_3P{=}C}\begin{matrix}\mathrm{CH_2R^2}\\ \mathrm{C(O)R^1}\end{matrix} \qquad \mathrm{R{=}Ph,\ OEt} \tag{2.206}$$

Strendman applied this reaction to the synthesis of several phosphorus ylides bearing different heterocyclic groups on the ylidic carbon atom (Scheme 2. 52). The latter were then used as starting compounds in the Wittig reaction[388]:

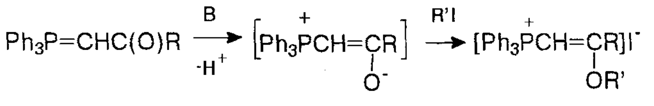


Scheme 2.52

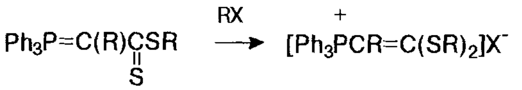
Reaction of phosphorus ylides with Mannich bases (Eq. 2.206)[388]

A solution of Mannich base (0.1 mol) and phosphorus ylide (0.1 mol) in toluene (500 mL) was heated under reflux for 6–7 h under nitrogen. The mixture was chilled and the crystalline product was removed by filtration and washed with cold toluene and petroleum ether. Analytical samples were prepared by recrystallization from ethyl acetate.

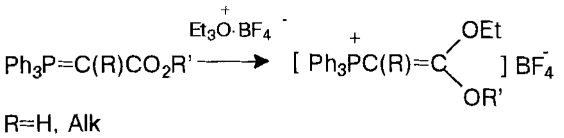
The alkylation of ylides bearing acyl or thioacyl groups on the α carbon proceeds with the formation of C- or S-substituted vinylphosphonium salts. Sometimes these could be isolated successfully and then used in organic syntheses (Eq. 2.207,208)[140,389,390]: C-alkoxycarbonylstabilized phosphorus ylides are alkylated with triethyloxonium tetrafluoroborate resulting in O-substituted 2-alkoxy-2-ethoxyvinyl-triphenylphosphonium tetrafluoroborate which after treatment with a base (R = H) is converted into the cumuleneylide (Eq. 2.209):[391]



$$\mathrm{Ph_3P{=}CHC(O)R} \xrightarrow[\mathrm{-H^+}]{\mathrm{B}} \left[\mathrm{Ph_3\overset{+}{P}CH{=}\underset{O^-}{C}R}\right] \xrightarrow{\mathrm{R'I}} [\mathrm{Ph_3\overset{+}{P}CH{=}\underset{OR'}{C}R}]\mathrm{I^-} \tag{2.207}$$



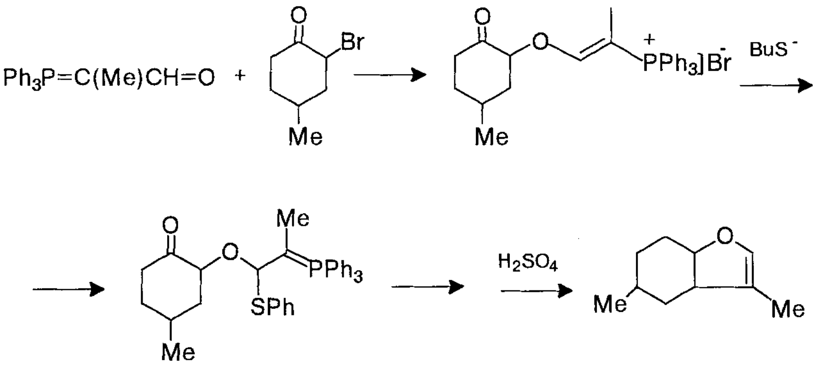
$$\mathrm{Ph_3P{=}C(R)\underset{\underset{S}{\|}}{C}SR \xrightarrow{RX} [Ph_3\overset{+}{P}CR{=}C(SR)_2]X^-} \tag{2.208}$$



$$\mathrm{Ph_3P{=}C(R)CO_2R' \xrightarrow{Et_3\overset{+}{O}\cdot BF_4^-} [\,Ph_3\overset{+}{P}C(R){=}C(OEt)(OR')\,]\,BF_4^-} \tag{2.209}$$

R=H, Alk

C-Alkylation of triphenylphosphonium α-formylalkylides with α-bromoketones has been proposed as a one-pot method for preparation of furans. The method includes the reaction of vinylphosphonium salts with butylmercaptide, intramolecular Wittig reaction and the desulfurization of the reaction product with mercury sulfate (Scheme 2.53)[386].



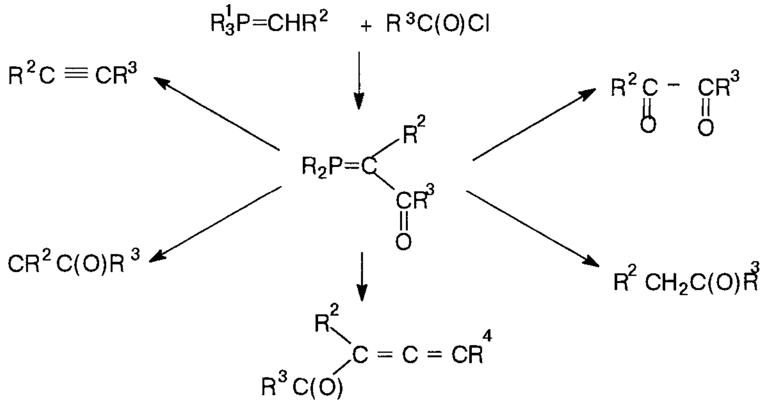
Scheme 2.53

2.3.3.2 Reactions with Acylation Reagents

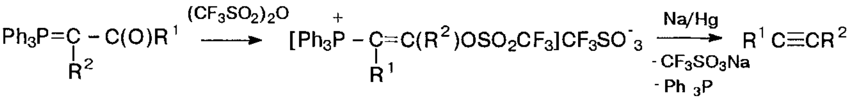
Acylation of phosphorus ylides is one of the most widely explored methods of using ylides for constructing carbon frameworks. Acylation of phosphorus ylides in combination with oxidation, hydrolysis, thermolysis, alkylation, and the Wittig reaction can be used to obtain ketocarboxylic acid derivatives, alkenes, alkynes, unsaturated carboxylic acids, allenes etc. (Scheme 2.54).

Acyl halides, anhydrides, esters, thioesters, and telluroesters of carbonic acids are used as acylating reagents[393].

Thus, Bestmann and coworkers developed a simple method for the preparation of acetylene derivatives by acylation of ketoylides with trifluorosulfonic acid anhydride, furnishing O-substituted vinylphosphonium salts, and by subsequent treatment of these compounds with sodium amalgam (Eq. 2.210)[394,395].

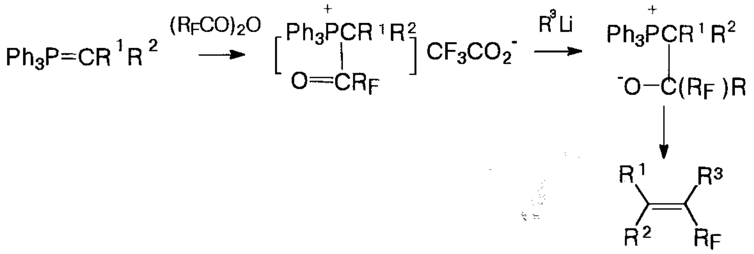


Scheme 2.54



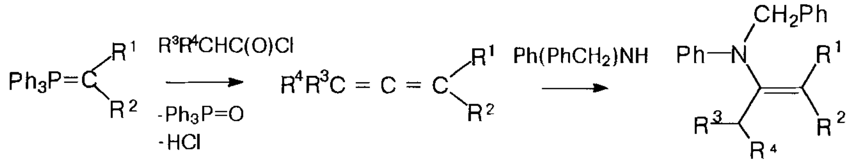
$$\mathrm{Ph_3P{=}\underset{R^2}{C}-C(O)R^1 \xrightarrow{(CF_3SO_2)_2O} [Ph_3P-\underset{R^1}{C}{=}C(R^2)OSO_2CF_3]^{+}CF_3SO_3^{-} \xrightarrow[-CF_3SO_3Na,\ -Ph_3P]{Na/Hg} R^1C{\equiv}CR^2} \qquad (2.210)$$

Acylation of P-ylides with perfluoroanhydrides was used to prepare substituted fluoroalkenes in the synthesis shown in the Scheme 2.55[396–398]:



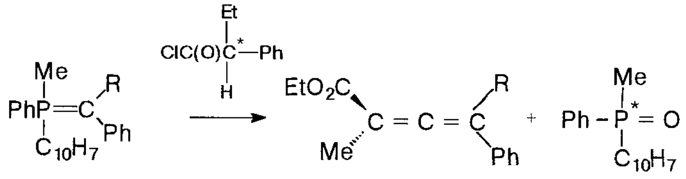
Scheme 2.55

Bestmann was the first to find that reaction of stabilized disubstituted phosphorus ylides with acyl halides led to the formation of phosphonium salts, which on heating eliminated phosphine oxide to afford allenecarboxylic acid derivatives.[181,399,399b,400] In recent years this method has been intensively studied for the preparation of allenes.[181,399b,399c,400] Marshall used the reaction for stereospecific preparation of butenolides[399b]. Sinibaldi and coworkers developed the synthesis of β-aminoesters and lactones by Michael addition of *N*-benzylaniline to allenic esters (Scheme 2.56, Table 2.14)[399c]. Ding and coworkers reported a new one-pot synthesis of fluorinated bromoallenes by reaction of triphenylphosphonium pentafluorophenylmethylide with bromoacetyl bromide[181].



Scheme 2.56

Bestmann and coworkers have shown that the reaction of triphenylphosphonium ylides with an optically active acyl chloride proceeds with asymmetric induction to provide enantiomerically enriched allenecarboxylates and an optically active phosphine oxide (Eq. 2.211)[401]:



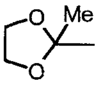
R=Me, Et

(2.211)

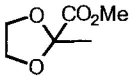
Table 2.14. Allenecarboxylic acid derivatives (Scheme 2.56)

R^1	R^2	R^3	R^4	Yield (%)	Ref
CO_2Et	Me	c-C_5H_9	H	95	399b
CO_2Et	CH_2CN	$PhCH_2CH_2$	H	83	399c
Ph	Et	EtO_2C	Me	77.5	401
CO_2Et	Me	H	H	82	399
CO_2Et	Me	$(CH_2)_3CO_2Me$	H	58	400
R	C_6F_6	Br	H	-	181
CO_2Et	$CH_2CH{=}CH_2$	a	H	73	399c
CO_2Et	CH_2CN	b	H	82	399c
$R^1 + R^2$=c		$PhCH_2OCH_2$	H	62	399c

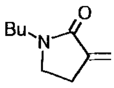
a=



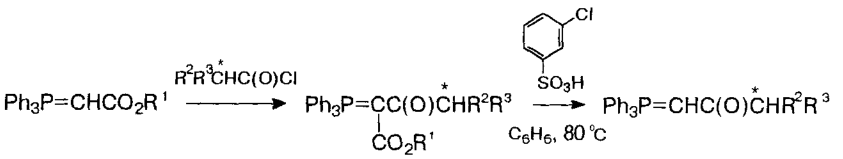
b=



c=



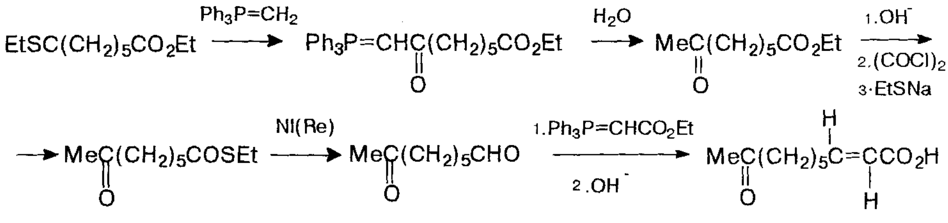
In other example, a route to the building block of the lateral chain of prostaglandins requiring a high optical purity, was realized via acylation of *tert*-butoxycarbonylmethylide with optical active acid chloride and subsequent decarboxylation of the phosphorus ylide (Eq. 2.212)[402]:



(2.212)

2.3.3.3 Examples in Natural Compound Synthesis

The acylation reaction proved well suited to the synthesis of several naturally occurring compounds, including the queen substance, found in the secretions of the honey bee (Scheme 2.57). Reaction of the thioester of heptane-1,7-dicarbonic acid with triphenylphosphonium methylide proceeds selectively at the thiocarbonyl group to give the acylated ylide. Hydrolysis of the acylylide afforded a ketoester, which was transformed into the ketothioester. Treatment of the ketothioester with Raney nickel in the presence of triphenylphosphonium methoxycarbonylmethylide causes desulfurization, furnishing the aldehyde. The latter reacts with triphenylphosphonium carboethoxymethylide to afford the ethyl ester of the queen substance, which was then hydrolyzed to yield the biologically active acid[324,403]:

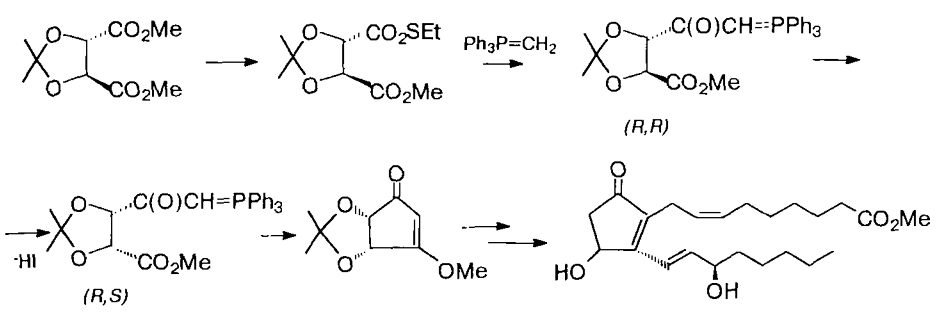


$$EtSC(CH_2)_5CO_2Et \xrightarrow{Ph_3P{=}CH_2} Ph_3P{=}CH\underset{\overset{\|}{O}}{C}(CH_2)_5CO_2Et \xrightarrow{H_2O} Me\underset{\overset{\|}{O}}{C}(CH_2)_5CO_2Et \xrightarrow[\substack{2.(COCl)_2\\3\text{-}EtSNa}]{1.OH^-}$$

$$\longrightarrow Me\underset{\overset{\|}{O}}{C}(CH_2)_5COSEt \xrightarrow{Ni(Re)} Me\underset{\overset{\|}{O}}{C}(CH_2)_5CHO \xrightarrow[2.OH^-]{1.Ph_3P{=}CHCO_2Et} Me\underset{\overset{\|}{O}}{C}(CH_2)_5\overset{H}{\overset{|}{C}}{=}\underset{\underset{H}{|}}{C}CO_2H$$

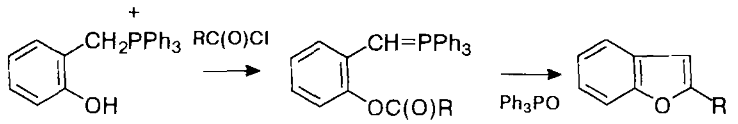
Scheme 2.57

The acylation of phosphorus ylides opens a route to optically active hydroxycyclopentenones, and naturally occurring cyclopentanoid compounds starting from accessible tartaric acid (Scheme 2.58)[404,405]. *R*,*R*-Tartaric acid monoester was converted into the thioether, reaction of which with triphenylphosphonium methylide gave the acylylide (Scheme 2.58). When the ylide was heated to 135°C at high pressure epimerization occurred at the chiral center next to the ylide function and intramolecular Wittig reaction furnished the acetonide of 4*R*,5*S*-dihydroxy-3-methoxy-2-cyclopentenone[395,405], a key compound in the enantioselective synthesis of the acetonides of 3-alkyl-4,5-dihydroxy-2-cyclopentenones by regioselective 1,2- or 1,4-addition of organometallic reagents. They are also starting compounds for the preparation of prostaglandins[404,405]:

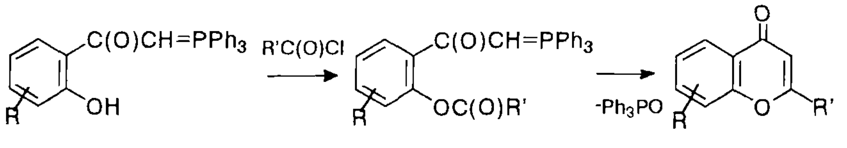


Scheme 2.58

The acylation of phosphorus ylides with carboxylic acid esters has been applied to the synthesis of cyclic compounds[407–413]. For example, Hercouet and Le Corre obtained different dihydrofurans and dihydropyrans from ω-acyloxy anhydrides (Eq. 2.213,214) [407–409]. This route has been used for the preparation of benzopyranones, flavones, and benzothiophene derivatives (See Chapter 6)[411, 413]:



(2.213)



(2.214)

2.3.4 Reactions with Compounds Containing Multiple Bonds

Phosphorus ylides react with a variety of multiple bonded compounds in addition reactions to afford betaine intermediates which produce new ylides by proton transfer. The most interesting are reactions of ylides with carbonyl compounds and with hetero analogs of carbonyl compounds (nitriles, azomethines, nitroso compounds and so on), the reactions of ylides with compounds bearing double and triple carbon–carbon bonds, the nucleophilicity of which depends on electron-withdrawing substituents (compounds with activated multiple bond). The reactions of phosphorus ylides with hetero analogs of carbonyl compounds are applied for the preparation of a number of important types of organic compound.

2.3.4.1 Compounds Containing Carbon–Carbon Multiple Bonds

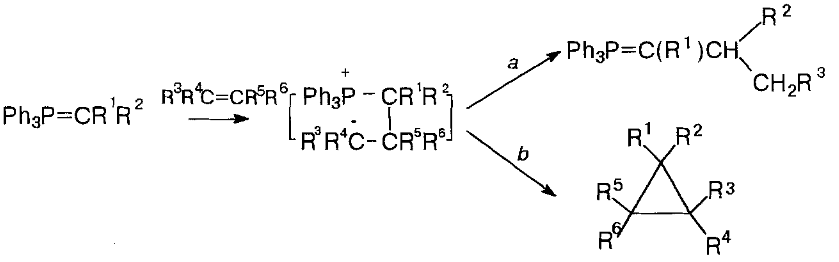
The reactions of phosphorus ylides with compounds containing multiple carbon-carbon bonds are very interesting theoretically and useful synthetically. Although phosphorus ylides do not react with isolated C=C and C≡C bonds, they readily undergo reactions with conjugated alkenes and alkynes, containing electron-accepting substituents.

Reaction with multiple carbon–carbon bonds are among those studied in most detail in the chemistry of the phosphorus ylides. Interest in this type of reaction is primarily a consequence of the preparative value of the products formed—derivatives of cyclopropane, pyran, cyclohexane, etc.

a) Alkenes—Synthesis of Cyclopropanes

Depending on the nature of substituents R^1 on the ylidic carbon atom and substituents R^2, R^3 on the multiple bond, the reaction of ylides with activated alkenes results in the formation of different products, in particular new C-alkylated ylides (Scheme 2.59, route a) or cyclopropanes (route b)[200b,209–216,415–430]. The reaction of stabilized phosphorus ylides with Michael acceptors is widely used for the preparation of new C-alkylated ylides (See Section 2.2.3

These two different directions of the reaction can be explained by one general mechanism—initial Michael addition via nucleophilic attack of the ylidic carbon atom on the electron-deficient carbon atom of the multiple bond resulting in the formation of the betaine. Transformations of betaine depend on the substituents R^1, R^2, and R^3:



a: R^1 or R^2 = electron-accepting substituents;
b: R^1, R^2 = electron-donating substituents.

Scheme 2.59

The betaine rearranges into an ylide if R^1 is an electron-accepting group which increases the mobility of the α proton. If, however, the R^1 group has positive inductive and mesomeric effects, when the mobility of the α proton is not sufficient for the prototropic rearrangement to the ylide, the reaction results in intramolecular expulsion of the triphenylphosphine with the formation of a cyclopropane (Table 2.15)[416].

Intermediate betaines have been isolated as individual compounds. Freeman[417] found that mesityl-β-styrylketone reacts with triphenylphosphonium methylide in ether to afford a salt-like betaine; this was isolated as colorless solid. Heating of the betaine to 115–120°C in xylene furnished 2-phenylcyclopropylmesitylketone in 50% yield (Eq. 2.215):

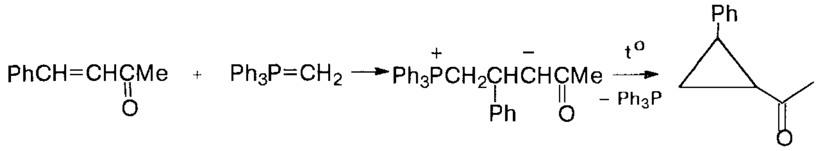
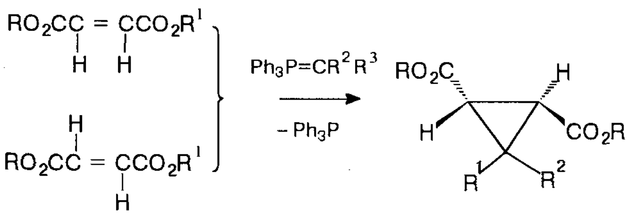

(2.215)

Table 2.15. Synthesis of cyclopropane derivatives from phosphorus ylides and alkenes (Scheme 2.59)

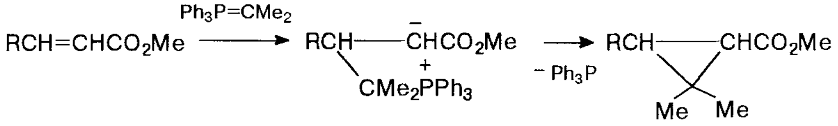
R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	Ref.
H	H	Ph	He	Mes	H	50	416
H	H	Me	He	O_2N	H	5	417
Me	Me	CO_2Et	H	CO_2Et	H	69	418
Et	Et	CO_2Et	H	CO_2Et	H	55	418
Me	Me	CO_2Me	H	3-$MeOC_6H_4$	H	65	420
Me	Me	CO_2Me	H	3-$MeOC_6H_4CH_2CH_2$	H	65	420
Me	Me	CO_2Me	H	Bu	H	65	420
Me	Me	CO_2Me	H	C_5H_{11}	H	65	420
Pr	H	Pr	H	R^5+R^6 = 9-Fluorenyl		65	422,423
$-CH_2(CH_2)_2CH_2-$		CO_2Et	H	CO_2Et	H	70	418
$-CH_2(CH_2)_2CH_2-$		CO_2Et	H	CO_2Et	H	65	418
Me	Me	$CH(OMe)_2$	H	CO_2Me	H	80	425
Me	Me	Pr	H	CO_2Me	H	46	421
Me	Me	CO_2Me	H	$(EtO)_2CH$	H	60	425,426
Me	Me	CO_2Me	H	$Me_2C=CH$	H	80	425-428
Me	Me	$(EtO)_2P(O)$	CO_2Me	PhCH=CH	H	80	429,430
H	Me	Me	H	CO_2Me	H	50	209
R^1+R^2 = c-Pr		Pr	H	R^5+R^6 = 9-Fluorenyl		65	423

Triphenylphosphonium alkylides react at room temperature with esters of fumaric and maleic acids with the formation of the appropriate *trans*-cyclopropane-1,2-decarboxylate in yields of 55–70%. The reaction is highly regio- and stereoselective (Scheme 2.60)[418]:

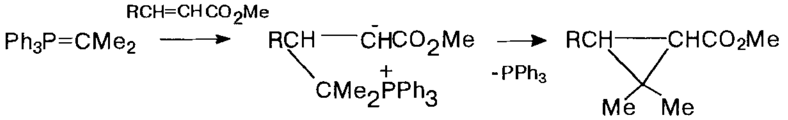

R^1, R^2=Me, Et.

Scheme 2.60

Grieco and Finkelhor[420] showed that the reaction of triphenylphosphonium isopropylide with α,β-unsaturated esters proceeds by formation of a betaine which readily eliminates the triphenylphosphine to furnish cyclopropanes in yields of 65–75% (Eq. 2.216,217). Krieff and Dubois investigated the influence of lithium salts on the ratio of cyclopropane diastereomers[421]. Mechoulam and Soundheimer[422] obtained spiro-9-fluorencyclopropane by reaction of fluorenone with excess triphenylphosphonium butylide; the reaction proceeds with a 2:1 ratio of starting reagents, because the triphenylphosphonium butylide reacts with fluorenone to afford the alkene which reacts with the ylide to furnish a cyclopropane (Eq. 2.218). The reaction scheme was confirmed in an independent experiment in which 9-butylidenefluorene was reacted with the triphenylphosphonium butylide resulting in the spiro-9-fluorenecyclopropane in good yield.

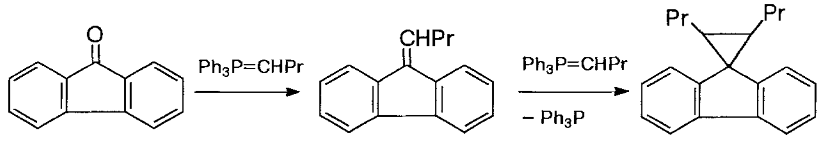


(2.216)



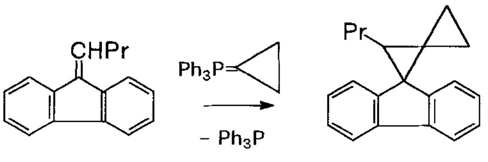
(2.217)

R= 3-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$CH$_2$CH$_2$, Bu, C$_5$H$_{11}$



(218)

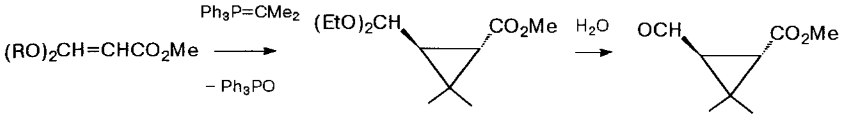
The reaction of 9-butylidenefluorene with triphenylphosphonium cyclopropylide furnishes the *bis*-cyclopentane derivative in 65% yield; this was isolated as a crystalline substance (Eq. 2.219)[423]:



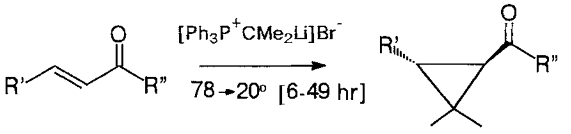
(2.219)

The reaction of phosphorus ylides with 4-oxobutenic acid esters was used for the preparation of chrysanthemic acid derivatives, starting compounds in the synthesis of pyrethroids. The reaction of triphenylphosphonium isopropylide with acetal methyl *trans*-oxobutenoate affords a derivative of cyclopropanecarboxylic acid, hydrolysis of which furnishes chrysanthemic aldehyde (Eq. 2.220)[418,419,424]. Reaction of triphenylphosphonium isopropylide with methyl *trans*-4-oxobutenoate in 2.4:1 reagent ratio proceeds in tetrahydrofuran with gradual rise of the reaction temperature from –

78 to 20°C. The methyl *trans*-chrysanthemate was obtained in 60% yield with 98% stereochemical purity[425]. Krieff and Dubois recently prepared cyclopropane carboxylates and cyclopropane amides by this method and studied the influence of lithium salts on the stereoselectivity of the reaction (Eq. 2.221)[426]:



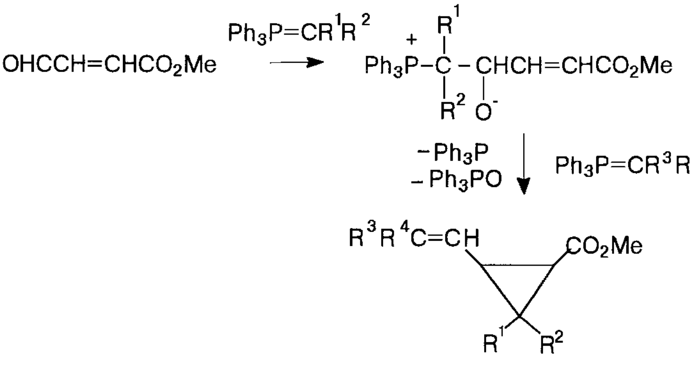
(2.220)



(2.221)

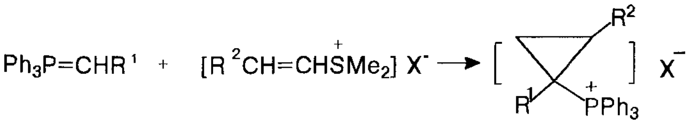
R=Pr, Ph; R'=OMe, NMe2

It was found that 4-oxobutenoate reacts with ylide to form a betaine which reacts with a second molecule of ylide to afford a bis-betaine. Elimination of triphenylphosphine and of triphenylphosphine oxide from this intermediate furnishes chrysanthemic acid derivatives[427]. Successive treatment of methyl 4-oxobutenoate with two different phosphorus ylides enabled the development of a one-pot synthesis of chrysanthemic acid esters bearing different substituents R^1, R^2, R^3, R^4 (Scheme 2.61)[427,428]:



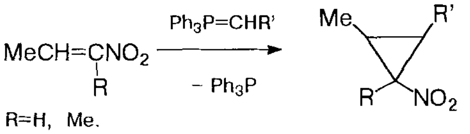
Scheme 2.61

The reaction of phosphorus ylides with vinylsulfonic salts in THF at 20–65°C for 10–12 h affords cyclopropyltriphenylphosphonium salts in 75–87% yields (Eq. 2.222)[431]:

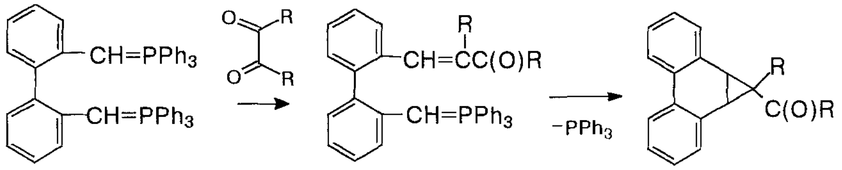


(2.222)

Triphenylphosphonium methylide reacts with conjugated nitroalkenes in dimethyl sulfoxide at 10°C to furnish nitrocyclopropanes in low yield (Eq. 2.223)[212,213]. Diphenyl-bis(triphenylphosphonium methylide) reacts with 1,2-diketones to give the ylide-alkene, which undergoes intramolecular addition of P=C and C=C bonds to afford dibenzonorcardiene derivatives in 25–60% yields (Eq. 2.224)[432].

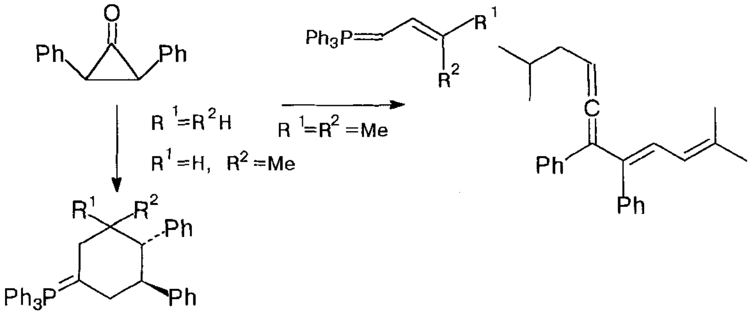


(2.223)



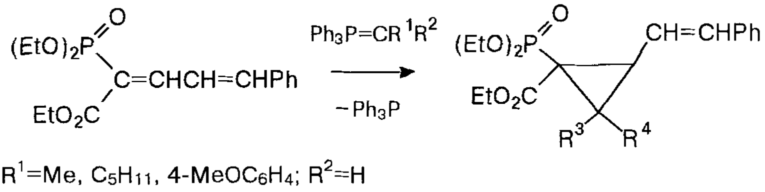
(2.224)

Reaction of 2*S*-*N*-benzoyl-2-*tert*-butyl-4-methylene-1,3-oxazoline-5-one with triphenylphosphonium isopropylide gave diastereomeric cyclopropanes, which were separated into the individual isomers and converted into enantiomerically pure *R*- and *S*-2,3-methanovaline[429b]. Allylic ylides react with diphenylcyclopropenone with the formation of new phosphorus ylides or allenes, depending on the substituents R^1, R^2 (Scheme 2.62)[433]:



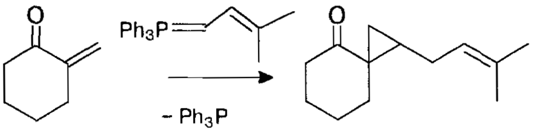
Scheme 2.62

Minami and coworkers[429] and then Bestmann and coworkers[430] used the reaction of dienophosphonate with triphenylphosphonium alkylides for the preparation of phosphorus analogs of chrysanthemic acid (Eq. 2.225):

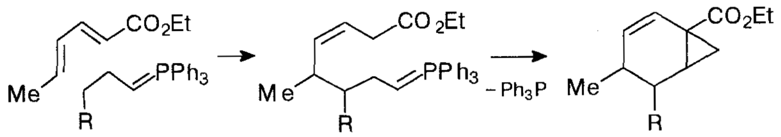


(2.225)

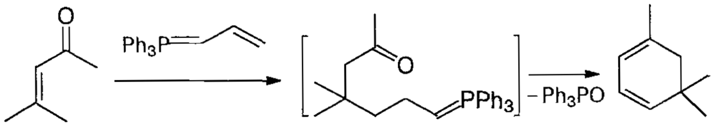
2-Methylcyclohexanone undergoes conjugate addition to phosphorus ylides producing cyclopropanes (Eq. 2.226)[434]: The reaction of allylic ylides with 2,4-alkadiene acid esters in tetrahydrofuran at room temperature affords norcarene-2 derivatives. The reaction proceeds via nucleophilic attack of the *g* carbon atom of allylide on the *d* carbon atom of the diene (Eq. 2.227)[435,436]: The reaction of mesityl oxide with triphenylphosphonium allylide results in 1,5,5-trimethylcyclohexa-1,3-diene in 50% yield; the formation of this compound can be explained by means of an intramolecular Wittig reaction (Eq. 2.228)[434]. Neff and coworkers[436] described the reaction of allylic ylides with α,β-unsaturated aldehydes, giving rise to dihydrobenzene derivatives. The reaction proceeds via Michael addition and intramolecular Wittig reaction (Eq. 2.229):



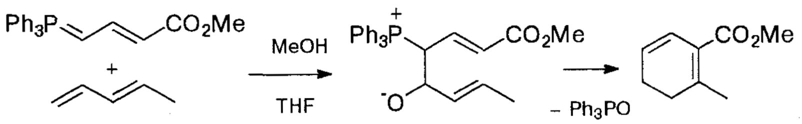
(2.226)



(2.227)

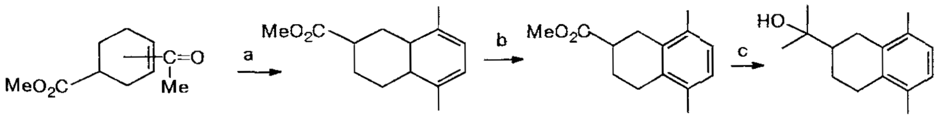


(2.228)



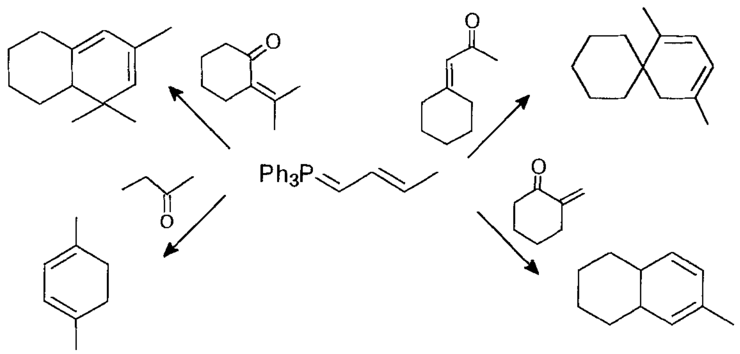
(2.229)

Dauben and coworkers[437] reacted allylides with conjugated alkeneketones to obtain a number of cyclohexadienes. This method has been used for the synthesis of the sesquiterpene derivative, occidole (Scheme 2.63). Carbomethoxycyclohexane reacted with triphenylphosphonium 2-butenolyde to afford the cyclohexane derivative, consecutive treatment of which with sulfuric acid and with methyllithium resulted in occidole (Scheme 2.64)[434]:



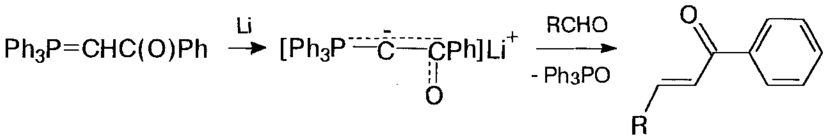
a= $Ph_3P{=}CHCH{=}CHMe$; b = H_2SO_4; c= MeLi

Scheme 2.63



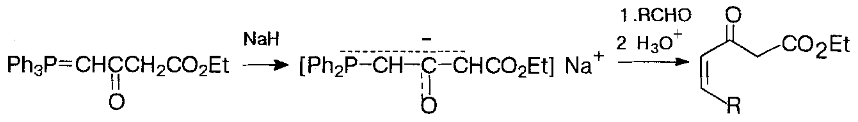
Scheme 2.64

Stabilized ylides, in particular α-ketoylides, have little activity toward conjugated alkenes. The activity of these ylides can, however, be increased by transformation into ylide-enolates. For example, triphenylphosphonium methylide reacts with aldehydes with difficulty and does not react with ketones. However the highly reactive ylide formed by reaction of triphenylphosphonium methylide with lithium in ylide-enolates, generated by treatment of the triphenylphosphonium phenacylide with lithium in hexametapol-benzene, alkenates aldehydes and ketones to produce dienones (Eq. 2.230)[438,439]:



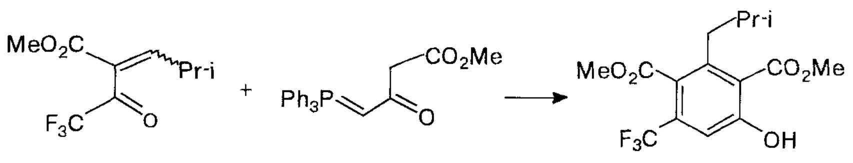
(2.230)

Although the reactivity of the stabilized ylide towards aldehydes was low, its sodium derivative readily entered into the Wittig reaction with carbonyl compounds to give conjugated unsaturated β-oxoesters of Z configuration in yields of 66% (Eq. 2.231)[440,441]:



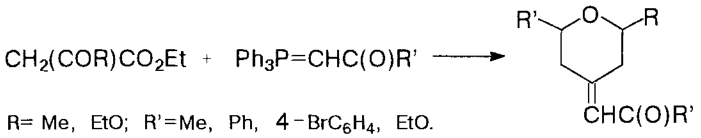
(2.231)

Treatment of a ketoester with an ylide resulting in the formation of a cyclization product with herbicide properties is shown in Eq. 2.232[442]:



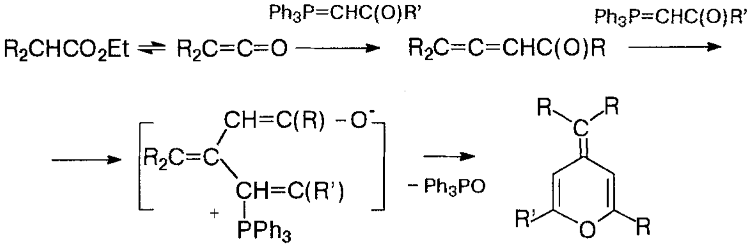
(2.232)

When β-dicarbonyl compounds (malonic ester, acetoacetic ester) are heated with alkylides in xylene they react to form pyrans in very good yields. The reaction proceeds via the formation of ketenes generated by thermolysis of the β–dicarbonyl compound. (Eq. 2.233)[443,444]:



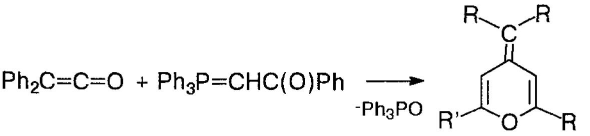
(2.233)

Ketenes undergo the Wittig reaction with ylides to form acylallenes, which add the second molecule of ylide to furnish pyran derivatives (Scheme 2.65)[445]:



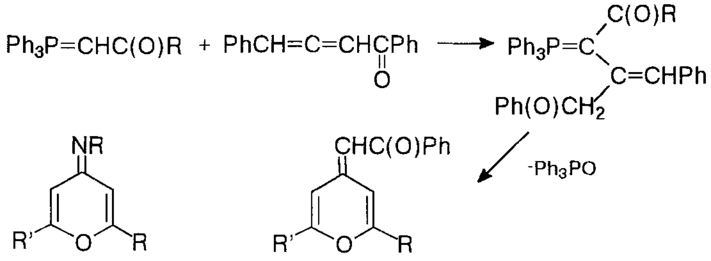
Scheme 2.65

Strzeletcka and Dupre[446] proved that this mechanism describes the reaction of diphenylketene with ylide (Eq. 2.234):



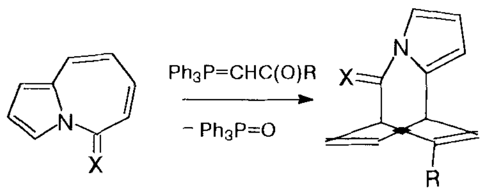
(2.234)

Alleneketones react with phosphorus ylides to afford 4-alkylidene-4*H*-pyrans and the analogous reaction of P-ylides with acylketenimines leads to the formation of 4-imino-4*H*-pyrans (Scheme 2.66)[447]:



Scheme 2.66

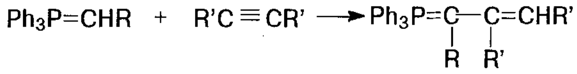
Reaction of aza-azulenes with stabilized ylides, in particular with triphenylphosphonium acyl-ylides, furnishes cyclohexane-1,4-diene derivatives. The reaction, reported by Fleitsch and coworkers[477], proceeds via the Michael addition of ylides to aza-azulenes (Eq. 2.235).



X=O, CHCN, CHC(O)Me (2.235)

b) Alkynes

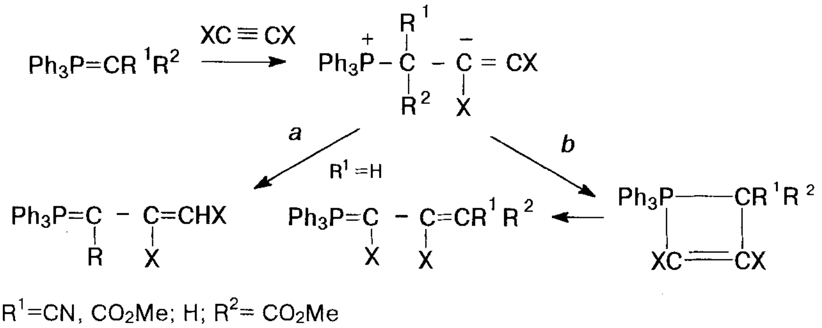
Hendrickson[445] and Trippett[175] were the first to report the reaction of phosphorus ylides with activated alkynes and obtained new C-alkylated ylides by this method (Eq. 2.236):



$$Ph_3P{=}CHR \;+\; R'C{\equiv}CR' \longrightarrow Ph_3P{=}\underset{R}{C}{-}\underset{R'}{C}{=}CHR' \qquad (2.236)$$

R=CN, R'=CO$_2$Me

Hendrickson and Trippett supposed that the reaction proceeds by Michael addition of phosphorus ylide to alkyne. Later, however, Brown and Bestmann et al.[449,450] found, that the reaction proceeds in two directions, resulting in simple Michael-addition products (route a) and rearranged products, formed as a result of insertion of an alkyne group between the phosphorus and the ylidic carbon atoms of the starting ylide (route b). Evidently, in both cases the addition of ylide to alkyne gives an intermediate betaine which either undergoes a prototropic shift (when R^1 or R^2 = H) to afford an normal C-alkylated ylide or is converted into a four-membered cyclic product which rearranges into an isomeric ylide (Scheme 2.67):

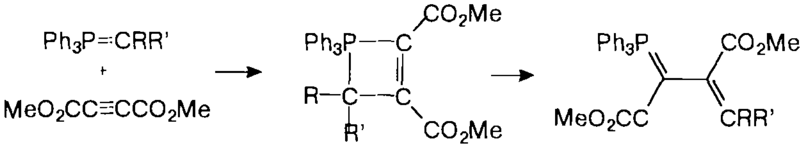


R^1=CN, CO$_2$Me; H; R^2= CO$_2$Me

Scheme 2.67

Intramolecular Michael additions have been described by Broess and coworkers[450]. C-Monosubstituted phosphorus ylides containing hydrogen atoms on the ylidic carbon atom react with activated alkynes in aprotic solvents with the formation of both Michael-addition and rearrangement products. The reaction of C-disubstituted ylides with alkyne derivatives usually results in rearranged products[279,449 461]. Thus Bestmann[449] and Brown[451] showed that reaction of a variety of phosphonium ylides with acetylenedicarboxylates leads to the formation of rearranged phosphorus ylides which must be formed via the four-membered cyclic intermediate. The structure of phosphorus ylide formed is not affected by changing the substituents R^1 and R^2 on the ylidic carbon atom (Eq. 2.239)

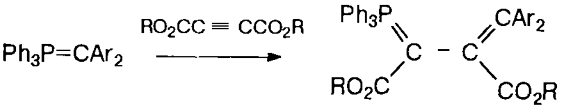
:



R=H, Me, Ph; R'=Me, Pr, Ph, CH=CHPh

(2.237)

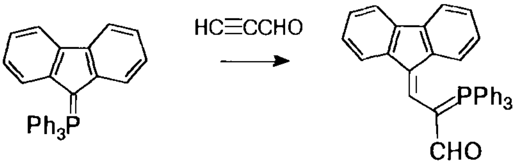
For instance, triphenylphosphonium diarylylides add to acetylenedicarboxylates to furnish ylides containing a lateral diarylmethylene group (Eq. 2.238)[451]:



Ar_2C= 9-fluorenyl, Ph_2C

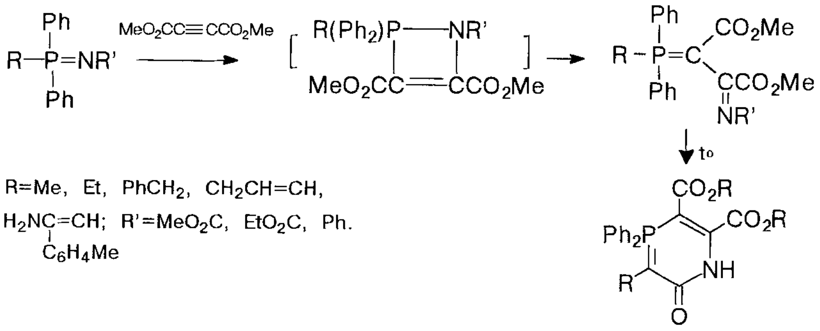
(2.238)

Ruder recently reported the influence of protic and aprotic solvents on the stereochemistry of the reaction of ketophosphonium ylides with acetylenedicarboxylates[452]. Braga and coworkers have synthesized a ylide bearing a CHO group on the *a* carbon atom by reaction of acrolein with triphenylphosphonium fluorenylide (Eq. 2.239)[453]:



(2.239)

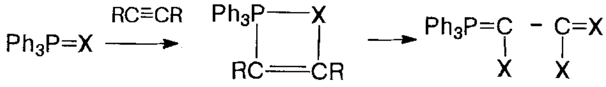
λ^5-Phosphazenes react with acetylenedicarboxylic acid esters similarly to phosphorus ylides. The reaction proceeds via the formation of the [2+2]-cycloaddition products which with cleavage of the P–N bond are converted into acyclic ylides. Heating results in the conversion of acyclic ylides to cyclic ylides (Scheme 2.68):[222,455]



R=Me, Et, $PhCH_2$, $CH_2CH{=}CH$,
$H_2N\underset{C_6H_4Me}{C}{=}CH$; R'=$MeO_2C$, EtO_2C, Ph.

Scheme 2.68

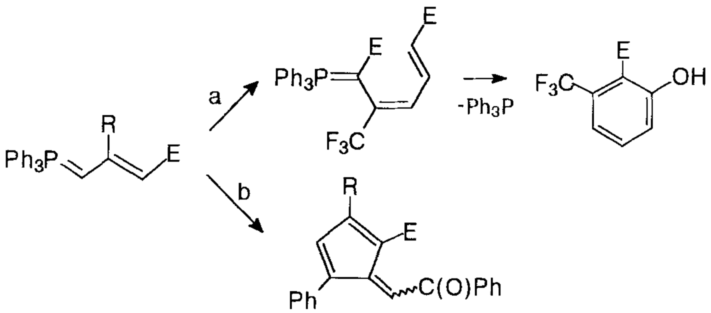
In 1970 Ciganek described what is so far the only example of reaction between triphenylphosphine oxide and dicyanoacetylene leading to the formation of phosphorus ylides (Scheme 2.69)[216]. Evidently insertion of an alkyne group into the P=X bond proceeding with the formation of ylides is characteristic of all three classes of tetracoordinate phosphorus compound—phosphine oxides, λ^5-phosphazenes, and phosphorus ylides. The driving force in this reaction is the formation of a highly stabilized conjugated phosphorus–carbon ylidic bond[456–458]:



X=O, NR', CR'_2; R=CN, CO_2Me

Scheme 2.69

Reaction of the methyl ester of trifluoromethylacetylenecarboxylic acid with γ-methoxycarbonylmethylide in dichloromethane results in a new rearranged ylide in 94% yield. When this ylide is heated under reflux in xylene it is converted into an ester of trifluoromethylsalicylic acid in 56% yield (Scheme 2.70, route a):[59–461].

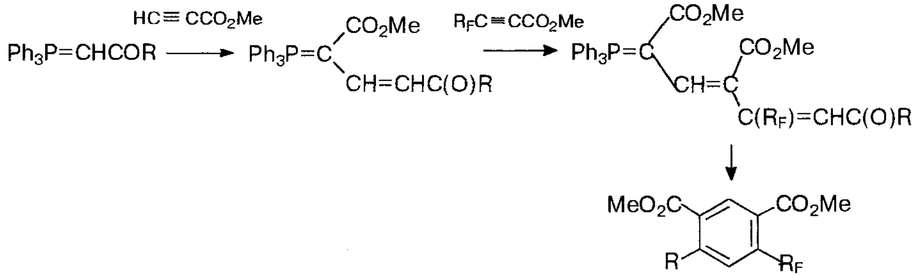


E=CO_2Et, a= $CF_3C{\equiv}CE$, R= H; b=$PhC(O)C{\equiv}CC(O)Ph$; R= H, Me

Scheme 2.70

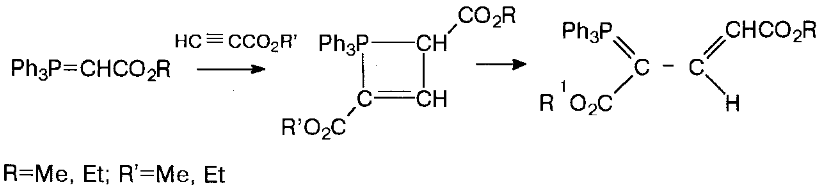
Hatanaka and coworkers proposed a new one-step synthesis of functionalized fulvenes by applying the reaction of allylylides with dibenzoylacetylene (Scheme 2.70, route b)[454]:

Ding's group described simple preparations of dimethyl 4-methyl-6-perfluoroalkyl-sophthalates and dimethyl 5-perfluoroalkylbiphenyl-2,4-dicarboxylates.[60,461] Methyl propionate reacts with monosubstituted *β*-ketoylides at 90°C to afford C-alkenylated ylides. When these ylides are introduced into a reaction with a second Michael acceptor, methyl perfluoroalkynoates, new ylides are formed which readily undergo the intramolecular Wittig reaction and are converted to dimethyl 5-perfluoroalkyl-biphenyl-2,4-dicarboxylates (Scheme 2.71)[462,463]:



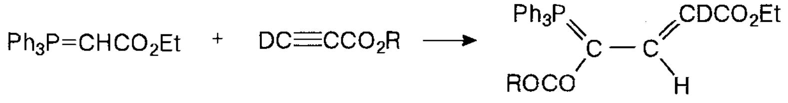
Scheme 2.71

The reaction of the triphenylphosphonium alkoxycarbonylmethylide with alkyl propionate in dichloromethane proceeds as a [2+2]-cycloaddition of the ylide to the triple bond to give a new phosphorus ylide (Eq. 2.240)[457,458]:

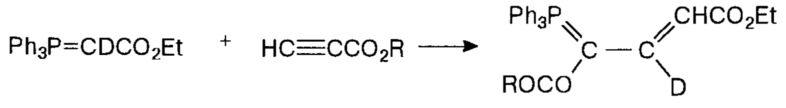


(2.240)

Shneider[458,464] developed a simple method for the introduction of deuterium to the *β*- or *γ*-carbon atoms of carbonyl-stabilized phosphorus ylides (Eq. 2.241,242):

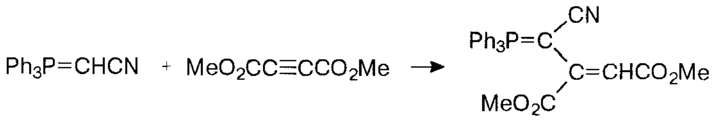


$$Ph_3P{=}CHCO_2Et + DC{\equiv}CCO_2R \longrightarrow (Ph_3P)(ROCO)C{=}C(CDCO_2Et)(H) \qquad (2.241)$$



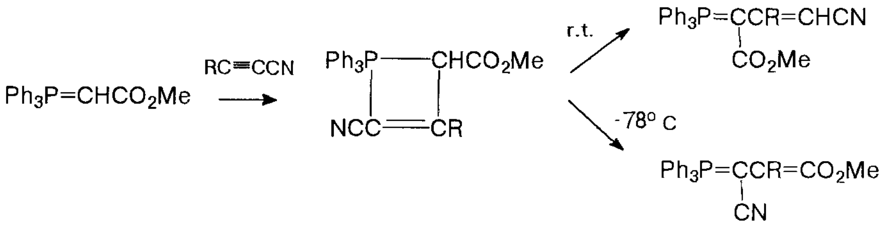
$$Ph_3P{=}CDCO_2Et + HC{\equiv}CCO_2R \longrightarrow (Ph_3P)(ROCO)C{=}C(CHCO_2Et)(D) \qquad (2.242)$$

Certain stabilized ylides containing hydrogen atoms on the α-carbon atom react with conjugate alkynes to give normal Michael addition products (Eq. 2.243)[445,459]:



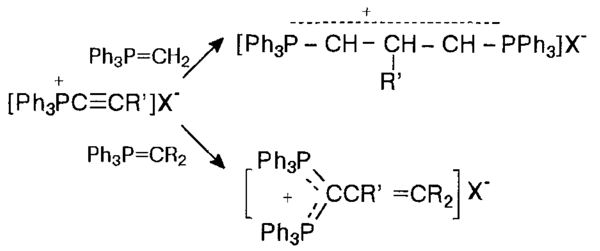
(2.243)

The reaction of phosphorus ylides with alkynes sometimes depends on the temperature. Thus Ding and coworkers[465] reported that the Michael addition of triphenylphosphonium carbomethoxymethylide to perfluoroalkylnitriles at –78°C leads to the formation of a rearranged ylide. At room temperature a mixture of rearranged and non-rearranged products was obtained (Scheme 2.72):



Scheme 2.72

Bestmann and Kisielowski[466] reported that Michael addition of triphenylphosphonium methylide to alkynetriphenylphosphonium salts leads to the formation of 1,3-bis(triphenylphosphonium)propenide salts, whereas reaction between benzylide or triphenylphosphonium isopropylide and alkynephosphonium salts furnishes stereospecifically the 1,1-diphosphaallylic salts (Scheme 2.73)[466]:



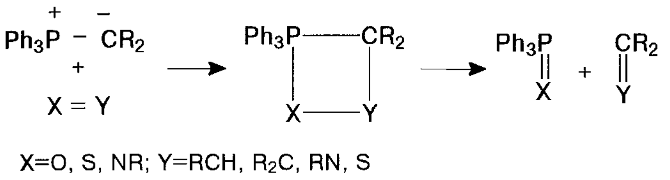
CR2=CHPh, CMe2

Scheme 2.73

N-Methylnitrilium triflate react with alkoxycarbonyl and aryl-stabilized phosphorus ylides to give unsaturated enamine phosphonium salts [224,465a,465b,465c].

2.3.4.2 Reactions with Compounds Containing Carbon–Heteroatom or Heteroatom–Heteroatom Multiple Bonds

This section covers reactions of phosphorus ylides with compounds containing carbon–heteroatom or heteroatom–heteroatom multiple bonds, i.e. C=O, C=S, C=N, S=O, N=N, and C≡N. The Wittig reaction is one example of reactions of this type (see Chapter 6). The initial step of this reaction is the nucleophilic attack of a carbanion on the atom of the multiple bond which bears a partial positive charge. The final step of the reaction includes elimination of triphenylphosphine oxide from the intermediate addition product (Eq. 2.244):

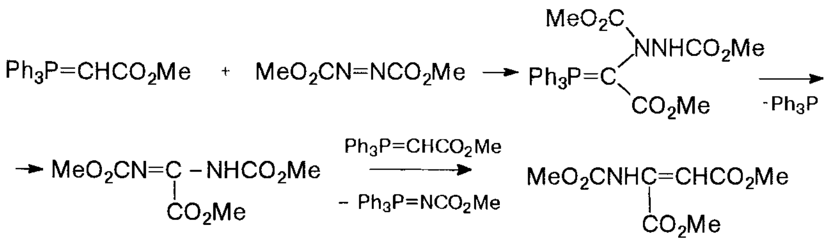


(2.244)

The reaction of phosphorus ylides with compounds containing C=S, S=N, S=O, or C=N groups proceeds analogously. The reaction of ylides with azo compounds and nitriles is similar to the reaction of ylides with alkenes and alkynes reviewed in the previous section.

a) Azo Compounds

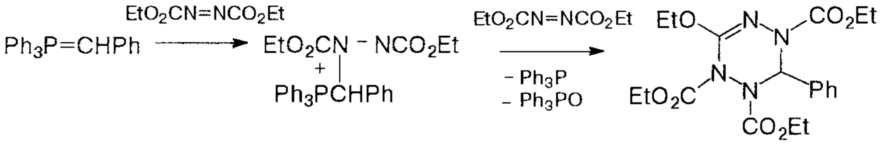
Because azo compounds are isoelectronic with alkenes, the reactions of both types of unsaturated compound with ylides are similar. Stable phosphorus ylides bearing an acyl or alkoxycarbonyl group on the *a* carbon atom, undergo the Michael addition to azodicarboxylic acid esters to form new phosphorus ylides. On heating these ylides eliminate triphenylphosphine to afford imino compounds, which react with excess starting ylide to produce dicarboxylates (Scheme 2.74)[467]:



Scheme 2.74

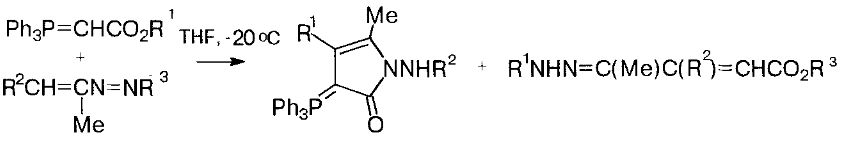
Non-stabilized and semistabilized ylides, in particular triphenylphosphonium benzylide, react with azodicarboxylates to provide 1,4,5,6-tetrahydrotetrazines.

Bestmann proposed a mechanism which explained the formation of 1,4,5,6-tetrahydrotetrazines (Scheme 2.75)[468]:



Scheme 2.75

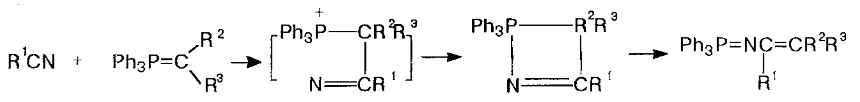
Attanasi and coworkers found that 1-amino-4-triphenylphospharanylidene-5-oxo-2-pyrrolines and *α,β*-unsaturated hydrazones were obtained in good yield by reaction of conjugated azoalkenes with ethoxycarbonylmethylene ylides. The structure of the compounds was determined by X-ray crystallography (Eq. 2.245)[469].



(2.245)

b) Nitriles—Synthesis of Ketones

The reaction of phosphorus ylides with nitriles is accompanied by insertion of a C≡N group between the phosphorus and the carbon atoms of the P=C bond to result in iminophosphoranes[455,216a]. Evidently the nucleophilic attack of the ylidic carbanion on the *sp* hybridized carbon atom of the nitrile group affords betaine which rearranges via a four-membered cyclic intermediate into an iminophosphorane (Eq. 2.246, Table 2.16):



(2.246)

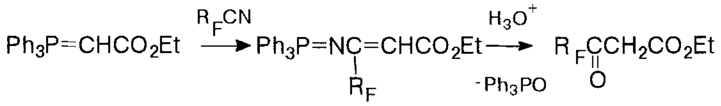
Table 2.16. Reaction of phosphorus ylides with nitriles (Eq. 2.246)

R^1	R^2	R^3	Yield (%)	Ref.
2-Furyl	Ph	H	65	455
2-Thiophenyl	Ph	H	60	455
Ph	Ph	H	–	455
2-Py	Ph	H	83	455
CF_3	CO_2Me	H	94	216a
CF_3	CN	H	84	216a
CF_3	CO_2Me	Me	100	216a
CF_3	COPh	Me	81	216a

The reaction of phosphorus ylides with nitriles combined with acidic hydrolysis of the addition product is a convenient method for the preparation of ketones (Eq. 2.247)[216a]:

$$Ph_3P{=}CHR \xrightarrow{R'CN} Ph_3P{=}NC(R'){=}CHR \xrightarrow{H_2O} R'C(O)CH_2R \qquad (2.247)$$

Trabelsi and coworkers[470] reported that reaction of triphenylphosphonium carboethoxymethylide with perfluoronitriles furnishes perfluoroalkyl-containing λ^5-phosphazenes in almost quantitative yields. The acid-catalyzed hydrolysis of these compounds led in very high yield to the formation of perfluoroalkyl-β-ketoesters which exist as keto–enol tautomers (Eq. 2.248):



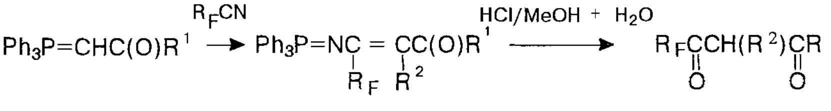
$$Ph_3P{=}CHCO_2Et \xrightarrow{R_FCN} Ph_3P{=}N\underset{R_F}{\underset{|}{C}}{=}CHCO_2Et \xrightarrow[-Ph_3PO]{H_3O^+} R_F\underset{O}{\underset{\|}{C}}CH_2CO_2Et \qquad (2.248)$$

$R_F{=}C_5H_{11}$, C_7F_{15}

Ethyl dihydro-2,2-oxo-3-perfluorooctanoate (Eq. 2.248)[470]

Triphenylphosphonium carboethoxymethylide (6.76 g, 0.02 mol), absolute ether (20 mL) and perfluorohexanonitrile (6.9 g, 0,023 mol) were placed a 100-mL flask under inert gas and the mixture was heated for 15 h at 30°C. The solvent was then removed under reduced pressure reduced to furnish in the residue λ^5-phosphazene ($R_F = C_5H_{11}$) in quantitative yield. A mixture of methanol (20 mL), concentrated hydrochloric acid (20 mL) and water (20 mL) was added to the residue and the mixture was heated under reflux for 2 h. The reaction product was then cooled and removed by filtration. After distillation under vacuum the β–ketoester was obtained in 85% yield, bp 95°C (1 mm Hg).

By this method were synthesized perfluoroalkyl-β-diketones which are good complexing agents, allowing the preparation of stable chelate complexes of many metal cations. The yields of perfluoroalkyl-3-diketones were approximately 90% (Eq. 2.249)[471]:



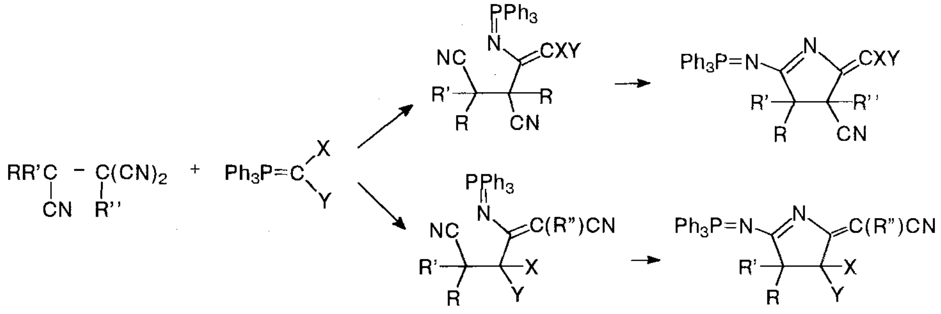
$$Ph_3P{=}CHC(O)R^1 \xrightarrow{R_FCN} Ph_3P{=}N\underset{R_F}{\underset{|}{C}} = \underset{R^2}{\underset{|}{C}}C(O)R^1 \xrightarrow{HCl/MeOH\ +\ H_2O} R_F\underset{O}{\underset{\|}{C}}CH(R^2)\underset{O}{\underset{\|}{C}}R \qquad (2.249)$$

$R^1{=}MeO$, EtO, Me, Ph; $R^2{=}Me$, Et, Pr, Bu, $CH_2{=}CHCH_2$;
$R_F{=}C_3F_7$, C_5F_{11}, C_7F_{15}.

The reaction of ylides with perfluoroalkylnitriles proceeds in chloroform at room temperature or under reflux. The yields of λ^5-phosphazenes were 85–97%. Hydrolysis of λ^5-phosphazenes by heating under reflux with hydrochloric acid in aqueous methanol furnished dicarbonyl compounds in 70–95% yields (Eq. 2.251)[472]:

The synthesis of λ^5-phosphazine (R^1= MeO, R^2 = Me, R_F-C_5F_{11}) (Eq. 2.251)
A mixture of triphenylphosphonium 2-carbomethoxymethylide (0.02 mol), perfluoropentanenitrile (0.022 mol) and chloroform (20 mL) was stirred at 40°C for 4 h. The solvent was then removed under vacuum and the residue was purified by column chromatography on silica gel 60, Merck, 70–230 mesh (50 g) with diethyl ether as eluent. Yield 94%.

Methyl-2-methyl-3-oxo-3-pentahexafluoroheptylpropanoate (Eq. 2.251)
A solution of the λ^5-phosphazene prepared in the previous experiment (11.15 g, 0.015 mol) in methanol (20 mL) was mixed with a solution of hydrochloric acid (20 mL) in water (20 mL). The mixture was heated under reflux for 3 h. After filtration the β–ketoester was obtained in a sufficiently pure state. Yield 0.7 g (92%), bp 95°C (0.01 mmHg), n_D^{20} 1.3407.

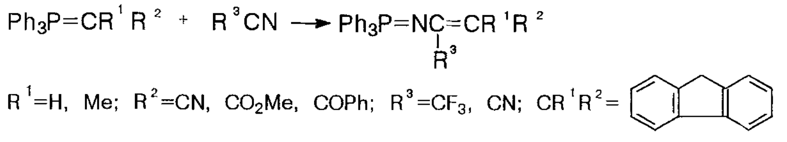


Scheme 2.76

The presence of lithium salts in the reaction medium increases the yields of the ketones. The lithium ion, acting as a Lewis acid, probably activates the nitrile group[473]. McEwen studied this reaction with optically active ylides. He found that the action of water on the intermediate betaine proceeds with inversion of configuration at the phosphorus atom[474].

Cadreau and Foucaud[475,476] reported that polynitriles react with ylides to afford iminophosphoranes which then undergo intramolecular cyclization (Scheme 2.76):

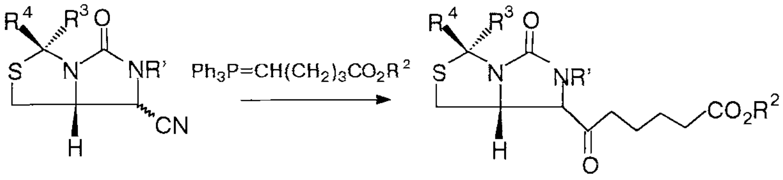
Non-stabilized phosphorus ylides react readily with both active and non-active nitriles to afford ketones after hydrolysis (Eq. 2.250). Although stabilized ylides do not react with non-active nitriles, they react smoothly with highly reactive nitriles such as dicyan or trifluoroacetonitrile[216a]:



$$Ph_3P{=}CR^1R^2 + R^3CN \longrightarrow Ph_3P{=}N\underset{\displaystyle R^3}{\underset{|}{C}}{=}CR^1R^2 \qquad (2.250)$$

R^1=H, Me; R^2=CN, CO_2Me, COPh; R^3=CF_3, CN; CR^1R^2=

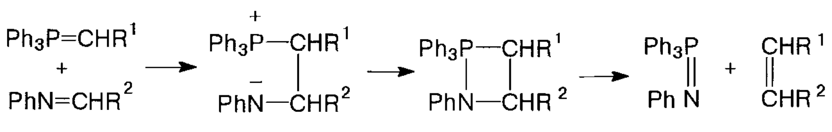
The biotin intermediates 7-(carboxyoxopentyl)imidazo[1,5-*c*]triazol-5-ones were prepared by treatment of nitriles with phosphorus ylide (Eq. 2.251)[477]:



(2.251)

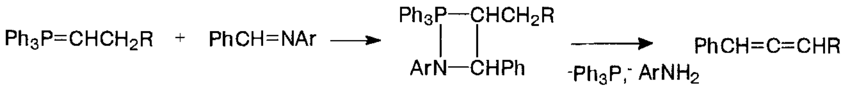
c) Imines

Imino compounds react with phosphorus ylides analogously to carbonyl compounds, i.e. by a Wittig-type reaction, to afford olefins and iminophosphoranes[161]. Because imines are less active toward phosphorus ylides than are carbonyl compounds, reaction of aldimines with ylides proceeds only upon heating to 110–180°C. There is little information about the reaction of ylides with ketimines, a reaction that occurs only under extreme conditions. Similarly to the Wittig reaction, the reaction of ylides with imines probably proceeds via an intermediate betaine and a four-membered cyclic azophosphetane, which decomposes into an olefin and λ^5-phosphazene (Eq. 2.252):



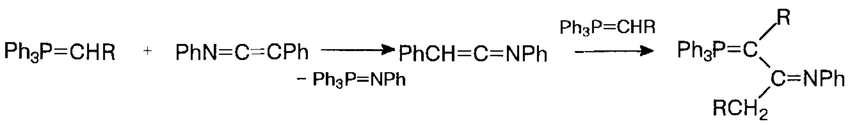
(2.252)

Ylides with a hydrogen atom on the β-carbon add imines with the formation of a stable betaine which only on heating eliminates triphenylphosphine and aniline to result in allenes[161]. These data confirm the mechanism mentioned above (Eq. 2.253):



(2.253)

The reaction between diphenylcarbodiimide and phosphorus ylides leads to the formation of ketimines and iminophosphoranes. Excess phosphorus ylide adds ketimine to result in a new phosphorus ylide (Eq. 2.254)[478]:



(2.254)

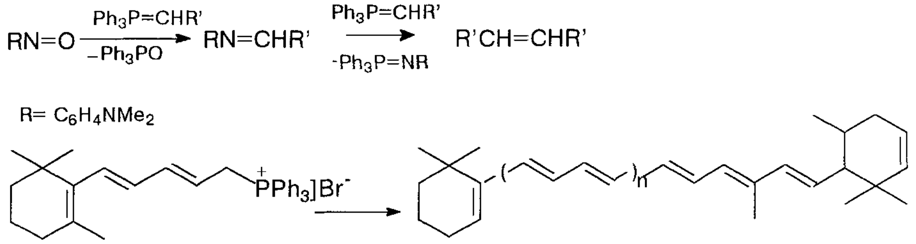
The reaction of imino compounds with phosphorus ylides is similar to the reaction of ylides with carbonyl compounds, but does not have any advantages. The reaction is of interest theoretically but is not used in organic synthesis.

d) Nitroso Compounds

Nitroso compounds react with phosphorus ylides in a Wittig-type reaction to afford imides and phosphine oxides (Eq. 2.255)[479–481]:

$$R_3P{=}CR'_2 + R''N{=}O \longrightarrow R''N{=}CR'_2 + R_3P{=}O. \qquad (2.255)$$

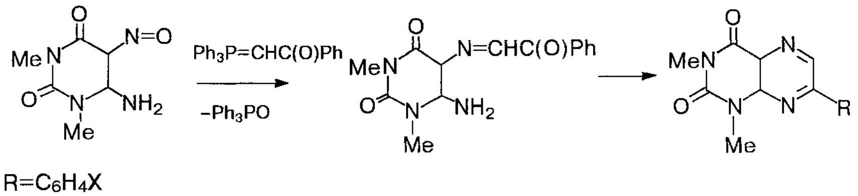
Schonberg and Brosowski[480] described the reaction of triphenylphosphonium fluorenylide with nitrosobenzene resulting in *N*-phenylfluoreneimine (Scheme 2.77). Nurrenbach and Pommer[481] found that reaction of phosphorus ylides with *N*-nitrosodimethylaniline leads to aldehydes and then to products of their condensation with a second molecule of phosphorus ylide. Azomethines were not obtained. The reaction between the ylide obtained from the axerophthiltriphenylphosphonium salt after its treatment with a base, and *N*-nitrosodimethylaniline furnishes β–carotene in 50% yield (Scheme 2.77)



$$RN{=}O \xrightarrow[-Ph_3PO]{Ph_3P=CHR'} RN{=}CHR' \xrightarrow[-Ph_3P=NR]{Ph_3P=CHR'} R'CH{=}CHR'$$

Scheme 2.77

Senga and co-workers used the reaction of phosphorus ylides with nitroso compounds to prepare heterocyclic compounds. 6-Amino-1,3-dimethyl-2,4-dioxo-5-nitrosohexahydropyrimidine reacts with triphenylphosphonium phenacylide to afford the imine which then undergoes intramolecular cyclization and dehydration to furnish 1,3-dimethyllumazine derivatives in 39–67% yields (Eq. 2.256)[482]:

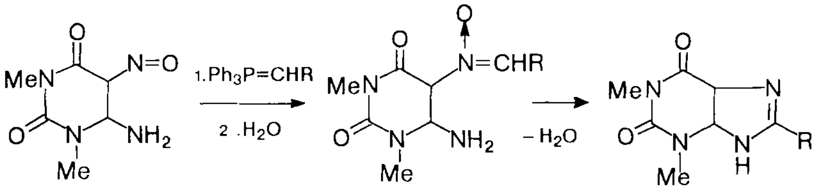


(2.256)

1,3-Dimethyl-7-phenyllumazine (Eq. 2.257)[482]

A solution of aqueous sodium hydroxide (10%, 0.5 mL) was added to a suspension of 6-amino-1,3-dimethyl-5-nitrouracil (0.5 mmol), phenacyl bromide (0.75 mmol) and triphenylphosphine (0.75 mmol) in tetrahydrofuran and the mixture was heated under reflux for 30 min. The solvent was then removed under vacuum, the residue was diluted with ethanol, and the 1,3-dimethyl-7-phenyllumazine was removed by filtration in 67% yield.

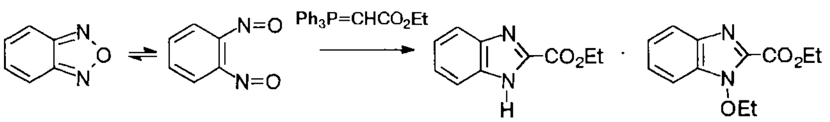
Derivatives of purine, pterozine, and pyrimidotriazine with physiologically active properties were obtained analogously. Eq. 2.257 shows the synthesis of one such compound, of 8*R*-theophiline[483]:



(2.257)

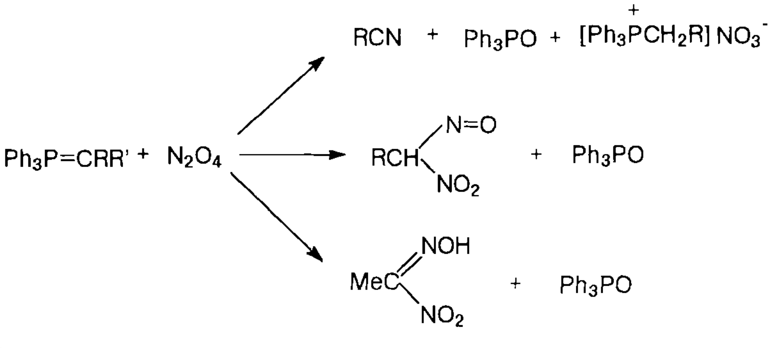
R=Ph, C_6H_4X-4, X=Me, Cl, NO_2; R=Ph, $C_6H_4Cl_2$-3,4

Reaction of triphenylphosphonium carboethoxymethylide with benzofuroxans, which exist in tautomeric equilibrium with *O*-dinitrosoarenes, leads to the formation of ethyl 2-benzymidazolcarboxylate and ethyl 1-ethoxy-2-benzymidazole (Eq. 2.258)[484]:



(2.258)

The reaction of phosphonium ylides with N_2O_4 was studied recently by Bestmann and coworkers.[141] The direction of the reaction is strongly influenced by the nature of the substituents on the starting ylide. The reaction furnishes nitriles (R = Ph, CO_2Et, COR; R′ = H). nitronitroso derivatives (R = Me, Et; R′ = CO_2Et) or nitrooximes (R = Me, R′ = H) (Scheme 2.78)



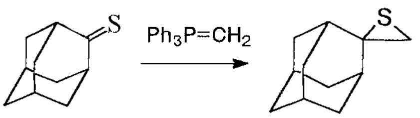
Scheme 2.78

e) Thioketones

Thiocarbonyl compounds usually react with ylides similarly to carbonyl compounds and several examples have been reported of the reaction of thiocarbonyl compounds with phosphorus ylides. For instance, Schollkopf found that diphenylthio-ketone reacts with triphenylphosphonium methylide to afford 1,1-diphenylethylene and triphenylphosphine sulfide (Eq. 2.259)[485,486]:

$$Ph_3P{=}CH_2 + Ph_2C{=}S \rightarrow Ph_2C{=}CH_2 + Ph_3P{=}S \qquad (2.259)$$

Exceptions are known, however. Thus, 2-adamantanethione reacts with the triphenylphosphonium methylide according to the Corey–Chaikovski reaction to result in *spiro*-adamantaneepisulfide and triphenylphosphine. The product of a Wittig-type reaction was not detected (Eq. 2.260)[487]:

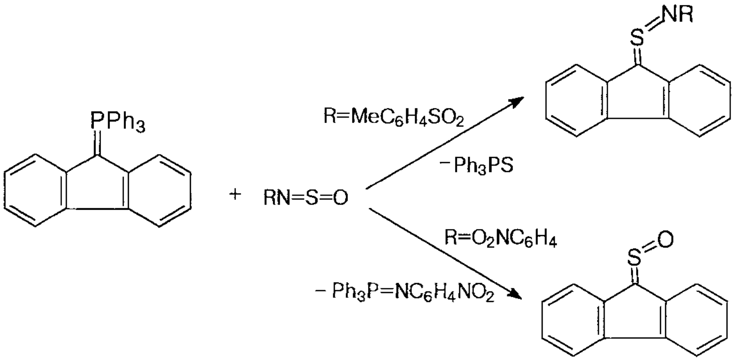


(2.260)

f) Compounds Containing an S=O Group

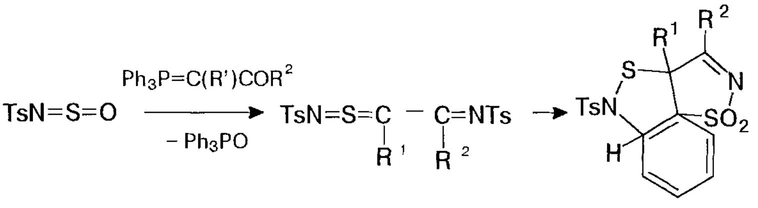
Saito and coworkers reported[488] that phosphorus ylides undergo the Wittig reaction with *N*-sulfinylamides. Depending on the substituents on the nitrogen, however, the reaction can proceed across S=N and S=O groups. For instance, the reaction of *N*-sulfinyltoluenesulfonamide with triphenylphosphonium fluorenylide occurred at the S=O bond with the formation of thione-S-ylide and triphenylphosphine oxide. At the same time the reaction of *N*-sulfonyl-*p*-nitroaniline with the ylide occurred at the N=S bond to result in sulfine and *p*-nitrophenyliminophosphorane (Scheme 2.79):

Stepanov and Chistokletov[553] reported that nitrilimines, prepared from the acylhydrazone chlorides and triethylamine add to phosphorus ylides to afford betaines existing in prototropic equilibrium with the starting phosphorus ylides. Treating solutions of ylides with various nitrile imides and nitrile oxides resulted in an extremely clean addition reaction leading to the corresponding pyrazoles and isoxazole derivatives.



Scheme 2.79

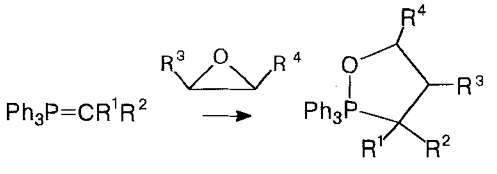
a-Acyl-substituted ylides undergo the Wittig reaction with *N*-sulfinyl-*p*-toluenesulfonamide, although in this case the thionyl-ylides formed are converted to *spiro*-tricyclic products by heating. The structure of the *spiro*-tricyclane was determined by X-ray crystallography (Eq. 2.261)[489]:



(2.261)

g) Oxiranes and Thiiranes—Synthesis of Cyclopropanes

Non-stabilized phosphorus ylides add to oxiranes with the formation of five-membered cyclic adducts, 1,2λ^5-oxaphospholanes, which were isolated as individual compounds.[72,289,425,491–500] Thus Wulff and Huisgen[492] reported the reaction of styrene oxide with triphenylphosphonium methylide. This reaction proceeds in ether at room temperature to afford crystalline 1,2λ^5-oxaphospholane in 71% yield. The reaction of enantiopure styrene oxide with P-ylides provides enantiomerically pure 1,2λ^5-oxaphospholanes.[490] The chemical shift, δ_P −55.2 ppm corresponds to the phosphorane structure of the cycloadduct. Bestmann and coworkers performed X-ray crystallographic analysis of 1,2λ^5-oxaphospholanes to show their five-membered cyclic structure with a trigonal-bipyramidal phosphorus atom. One phenyl group and the ring oxygen atom are apical ligands on phosphorus[491].

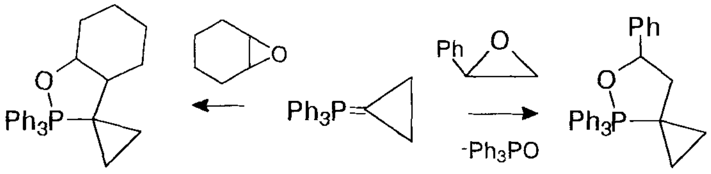


(2.262)

General method for the preparation of 1,2λ^5-oxaphospholanes by reaction of phosphorus ylides with oxiranes (Table 2.17, Eq. 2.262)[491]

A solution of oxirane (100 mmol) in THF (~75 mL) was mixed with a solution of the appropriate phosphorus ylide (100 mmol) in THF (~75 mL) and the reaction mixture was left at 20–45°C for ~24 h. The solvent was then removed under vacuum and the residue was dissolved in hexane. Recrystallization from hexane afforded 1,2λ^5-oxaphospholanes in 65–80% yield:

Bestmann and coworkers obtained crystalline *spiro*-1,2λ^5-oxaphospholanes in high yield by reaction of triphenylphosphonium cyclopropylide with cyclohexene oxide and styrene oxide (Scheme 2.80)[423]:

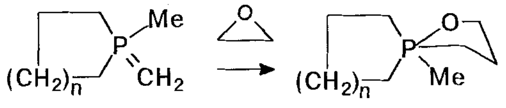


Scheme 2.80

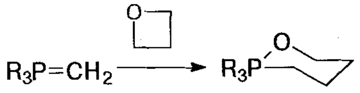
Table 2.17. 1,2λ^5-oxaphospholanes (Eq. 2.262)

R^1	R^2	R^3	R^4	Yield (%)	mp (°C)	Ref.
H	H	H	H	-	116–117	499
H	H	H	H	75	116	491
H	H	H	Me	80	123–124	490,491
H	H	H	Et	80	129–130	490,491
H	H	H	Ph	71	143–144	490,492
H	H	H	Ph	80	143	491
H	H	H	$CH(OEt)_2$	67	94–95	491
H	H	H	$CH(OMe)_2$	65	89–90	491
$R^1 + R^2 = CH_2CH_2$		H	Ph	80	155	423
$R^1 + R^2 = CH_2CH_2$		$R^3 + R^4 = c\text{-}C_6H_8$		86	165	423

The reaction of phosphorus ylides bearing an exocyclic P=C group with oxiranes proceeds under mild conditions to provide *spiro*-bicyclic phosphoranes in high yields (Eq. 2.263)[493] and the reaction of phosphorus ylides with oxetanes proceeds only on heating in sealed tubes to furnish the corresponding 2,2,2-*R*-substituted-1,2λ^5-oxaphosphorinanes (Eq. 2.264)[493]:



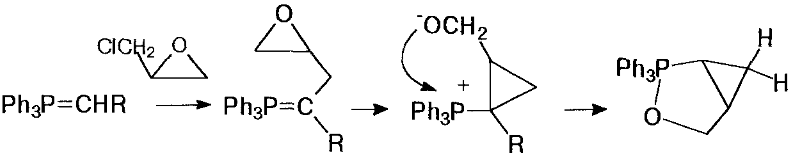
(2.263)



(2.264)

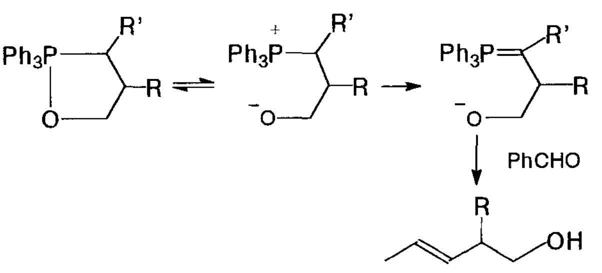
$R_3P = Me_3P$, $-CH_2(CH_2)_nCH_2-$,

Le Corre and coworkers[494,495] found that reaction of ylides with epichlorohydrin led to the formation of bicyclic compounds with oxaphospholane and cyclopropyl rings. The reaction proceeds with 2:1 ratio of ylide to epichlorohydrin. Evidently the initial step of the reaction is alkylation of the ylide by the epichlorohydrin followed by intramolecular attack of the ylidic carbon atom on the oxirane ring resulting in the cyclopropane oxaphosphetane (Eq. 2.265):



(2.265)

1,2λ^5-Oxaphospholanes, formed by reaction of ylides with oxiranes, exist in tautomeric equilibrium with hydroxy ylides, which undergo the Wittig reaction with carbonyl compounds [494–502]. According to NMR spectra oxaphospholanes have a ring structure in non-polar solvents whereas in polar solvents there is an equilibrium with an open-chain form (Scheme 2.81) [491] :

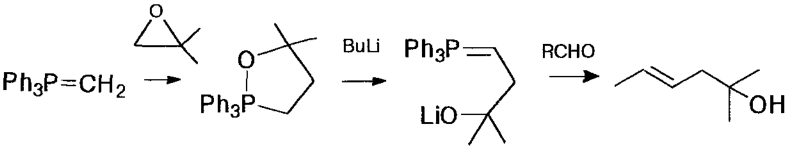


Scheme 2.81

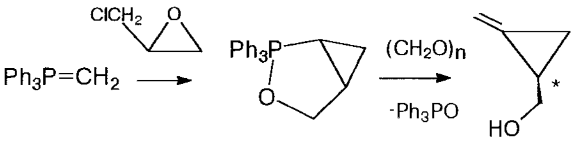
4-Phenylbuten-3-ol (Scheme 2.81)[499]

A mixture of oxaphospholane (R = R′ = H, 24 g) and benzaldehyde (8 g) was heated at 90°C for 2 h. The reaction mixture was then chromatographed on and aluminum oxide column (740 g). The column was first eluted with petroleum ether (1500 mL) then with benzene–petroleum ether (3:1). After evaporation of the solvent under reduced pressure 9.7 g of oil was obtained. This product was dissolved in ether and the solution was washed with an aqueous solution of sodium bisulfite, dried with sodium sulfate, and evaporated. The residue was distilled under vacuum. The yield of 4-phenylbuten-3-ol was 17.4 g (67%), bp 137–138°C (0.1 mmHg), n_D -1.5711.

Treatment of oxaphospholane with butyllithium generates active ylides bearing an epoxy group on the α-carbon atom (Eq. 2.266). These ylides are effective reagents for the preparation of homoallylic alcohols and are, therefore, widely used for the synthesis of naturally occurring compounds.[496–498,503] On heating with paraform-aldehyde oxaphospholanes react to form cyclic acetates in virtually quantitative yield[88].

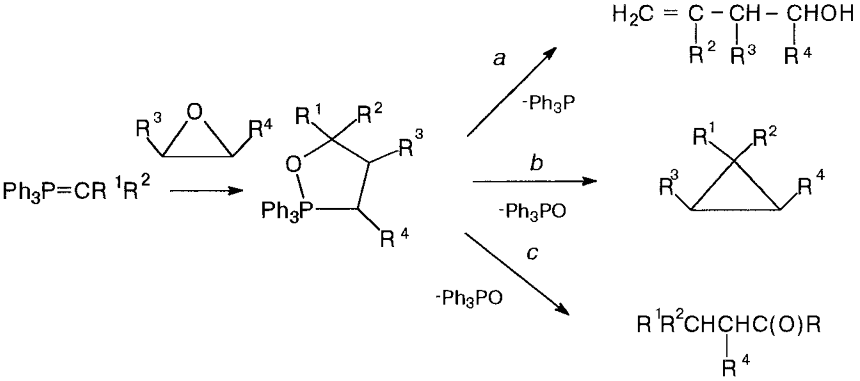


(2.266)



(2.267)

Enantiomerically pure *R* and *S* (methylenecyclopropyl)carbinols have been synthesized by one-pot reactions of triphenylphosphonium methylide with *R*- and *S*-epichlorohydrin, respectively, followed by addition of paraformaldehyde (Eq. 2.267)[503c]. Shweizer and coworkers[504] proposed a mechanism for the reaction of ylides with oxiranes which involves initial attack of the ylidic carbon atom on the epoxide ring with the formation of an oxaphospholane. The mechanism and stereochemistry of the reaction of γ-oxide ylides with aldehydes were reviewed by Maryanoff and Reitz[501].



Scheme 2.82

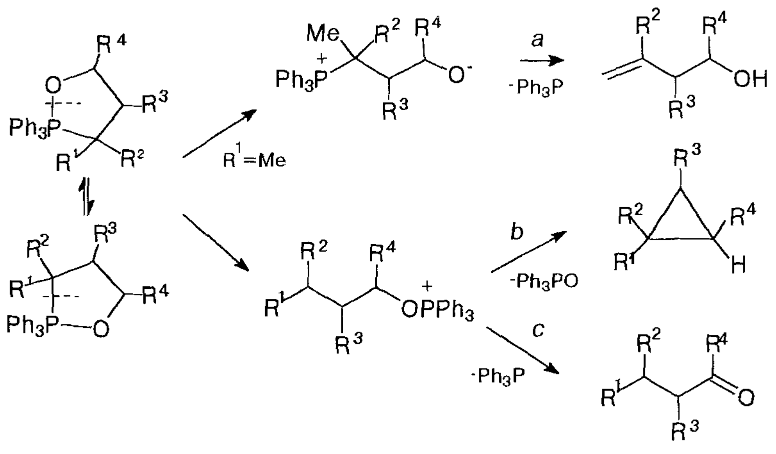
1,2λ^5-Oxaphospholanes formed by reaction of phosphorus ylides with oxiranes undergo various interesting transformations and are widely explored and useful reagents. Thus on heating they are converted into hydroxyolefins, ketones or cyclopropanes.(Scheme 2.82):

The regioselectivity of these thermal transformations depends on the nature of the substituents R^1, R^2, R^4 on the oxaphosphetane ring (Scheme 2.83):

(a) If the R^4 group is an electron acceptor the P–O bond occupies an apical position and cleaves to result in a betaine which eliminates triphenylphosphine and is converted into a hydroxyolefin.

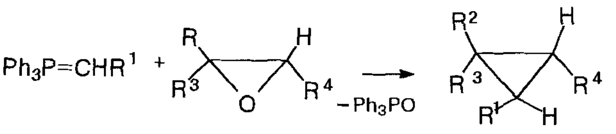
(b) If R^1 and R^2 are electron-acceptors which increase the apicophilicity of the *a* carbon atom the reaction results in a betaine which decomposes with the elimination of triphenylphosphine. Electron-accepting R^1 and R^2 groups stabilize the negative charge located on the lateral carbon atom thus favoring the elimination of triphenylphosphine oxide and the formation of cyclopropane.

(c) If R^3 is an electron-donating group this promotes the elimination of triphenylphosphine and the formation of ketone.



Scheme 2.83

The reaction of phosphorus ylides with oxiranes and alkenes is a convenient and useful method for the synthesis of cyclopropanes. Good yields of cyclopropanes were obtained by reaction of stabilized and semistabilized triphenylphosphonium ylides with different oxiranes (Eq. 2.268). For instance, triphenylphosphonium carboethoxymethylide reacts with cyclohexane oxide, 1-octene, and styrene oxide to give cyclopropane derivatives in 30–60% yields (Table 2.18). Denney and coworkers[505] found that the optically active styrene oxide and triphenylphosphonium carboethoxymethylide gave optically active ethyl *trans*-2-phenylcyclopropane carboxylate. The hydroquinone is a weak catalyst whereas boron trifluoride etherate, in contrast, inhibits the reaction:



(2.268)

Table 2.18. Preparation of cyclopropanes by reaction of phosphorus ylides with oxiranes (Eq. 2.268)

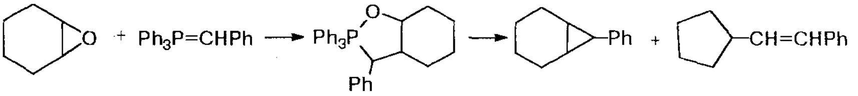
R^1	R^2	R^3	R^4	Yield (%)	Ref.
CO_2Et	H	H	Ph	30	505
CO_2Et	C_6H_{13}	H	H	46	505
CO_2Et	H	$-(CH_2)_4-$		63	505
CO_2Et	Ph	H	Ph	40–50	506
Ph	H	H	Ph	40	508

Ethyl trans-2-hexylcyclopropanecarboxylate (Eq. 2.268)[505]

A mixture of triphenylphosphonium carboethoxymethylide (17.6 g, 0.051 mol) and octene-1 oxide (19.5 g, 0.152 mol) was heated under reflux at 200°C for 8 h. The mixture was then fractionated under vacuum to provide 4.62 g (46%) of ethyl *trans*-2-hexylcyclopropanecarboxylate, bp 120°C (10 mmHg).

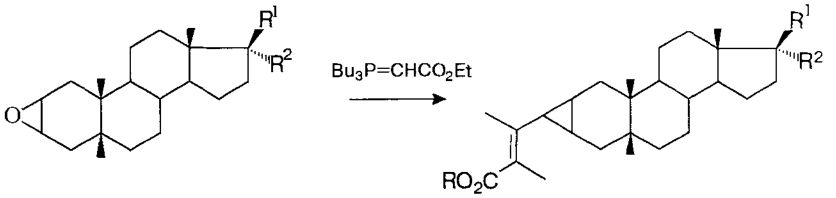
McEwen and Wolf[506a] reported that reaction of triphenylphosphonium carboethoxymethylide with oxiranes at 210–220°C resulted in cyclopropane-carboxylic acid esters in moderate yields. Walborsky[507] described the reaction of optically active phosphorus ylides with oxiranes proceeding with inversion of the configuration at the phosphorus atom. The results of this work were confirmed by McEwen and coworkers[506b,508] who in another paper reported that the reaction of α–styrene oxide with optically active methylethylphenyl-phosphonium benzylide proceeds with 50% inversion of the configuration at the phosphorus atom[506b].

α-Cyclohexene oxide reacts with triphenylphosphonium benzylide to afford 7-phenylnorcorane and 1-phenyl-2-cyclopentylethylene. The olefin is probably formed as a result of cleavage of the C–C bond in 1,2λ^5-oxaphosphetane to generate a carbonium ion which then undergoes rearrangement with reduction of the ring (Eq. 2.269)[510]:



(2.269)

This reaction has been used for conversion of 2,3-steroid oxiranes to the corresponding alkenes (Eq. 2.270)[511]:

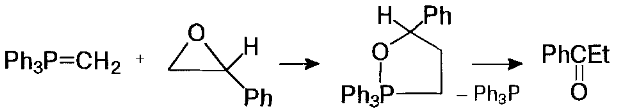


(2.270)

R=Et, Bu; R=C_8H_{17}, OC(O)Me, OCH_2CH_2O, OH; R=H, Me

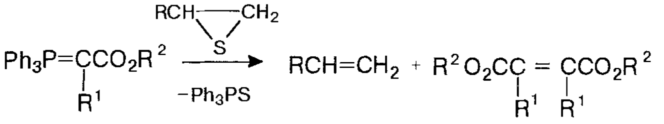
Taylor and co-workers described the reaction of stabilized P-ylides with 1,2-dioxines resulting in diastereomerically pure cyclopropanes.[509]

The reaction of P ylides with oxiranes results in the formation of ketones in good yields. For instance, thermolysis at 220°C of 2,2,2-triphenyl-5-phenyl-1,2λ^5-oxaphospholane, prepared by reaction of triphenylphosphonium methylide with styrene oxide, affords propiophenone in 66% yield (Eq. 2.271)[492]:



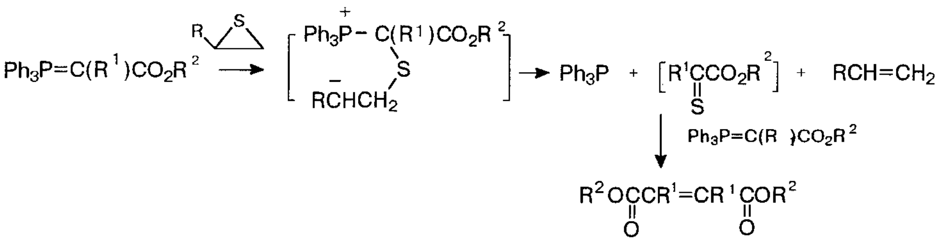
(2.271)

There is little information about the reaction of phosphorus ylides with episulfides. Okuma and coworkers[512] reported that stable phosphorus ylides react with episulfides to result in the formation of dialkylfumarates and dialkylsaleates in good yields (Eq. 2.272):



(2.272)

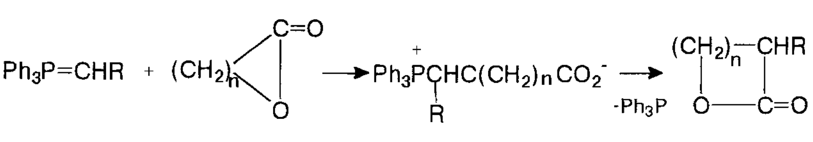
This reaction probably proceeds via attack of the ylide carbanion on the episulfide sulfur to result in thiocarbonyl compounds which undergo the Wittig reaction with the initial ylide to furnish olefins (Scheme 2.84)[512]:



Scheme 2.84

h} Reaction with Lactones

The reaction of non-stabilized triphenylphosphonium ylides with lactones furnishes triphenylphosphonium carboxylate betaines, the thermolysis of which proceeds with the elimination of triphenylphosphine to furnish provide new lactones containing an ylidic carbon atom in the ring (Eq. 2.273)[288,513-516]:



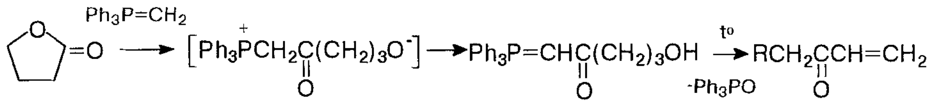
(2.273)

n=2, 3; R=H, Me

γ-Butyrolactone (Eq. 2.273)[513]

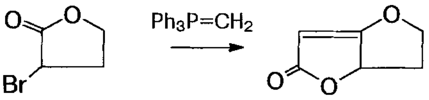
A solution of triphenylphosphonium methylide in THF (prepared from methyltriphenylphosphonium bromide and sodium amide in THF at 0°C) was added dropwise with stirring to a solution of *β*-propiolactone in the same solvent. After stirring for 0.5 h the hygroscopic betaine was removed by filtration (85% yield) and then heated at 220°C under nitrogen. The triphenylphosphine and *γ*-butyrolactone were obtained in 74% yield.

Bestmann[514] showed that sometimes triphenylphosphonium methylide reacts with β-lactones to afford ω-hydroxyketoylides, probably as a result of prototropic rearrangement of the betaine. Le Roux and Le Corre recently reported thermolytic conversion of these ylides to α,β-unsaturated ketones (Eq. 2.274)[513b]:



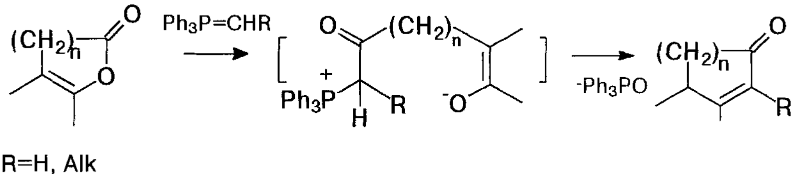
(2.274)

Brennan and Murphy reported that the reaction of non-stabilized phosphorus ylides with lactones proceeds at the carbonyl group to result, via an intramolecular Wittig reaction, in a bicyclic enol ether (Eq. 2.275)[513c]:



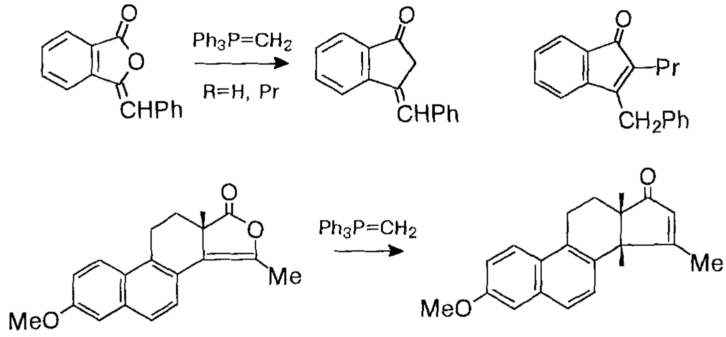
(2.275)

The reaction of phosphorus ylides with cyclic enol lactones is accompanied by elimination of triphenylphosphine oxide, resulting in the enones (Scheme 2.85)[515]: This reaction enables one-step conversion of cyclic enol lactones into α,β-unsaturated ketones (Scheme 2.85).



Scheme 2.85

Exposure of benzylidenephthalide to tri-phenylphosphonium methylide for 24 h at 23°C afforded 3-benzylydeneinden-1-one in 44% yield. Similarly, the reaction of benzylidene-phthalide with tri-phenylphosphonium methylide gave 3-benzyl-2-propylenin-denone in 30% yield. The tetracyclic enol lactone (±)-3-methoxy-15-methyl-16-oxaestra-1,3,5(10)6,8,14-hexaen-17-one reacts in THF with triphenylphosphonium methylide to give an α,β-unsaturated ketone only—(±)-3-methoxy-15-methyl-14β-estra-1,3,5(10)6,8,15-hexaen-17-one—in 60% yield[515]:



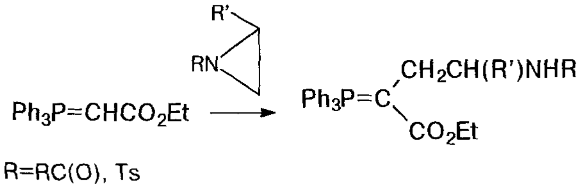
Scheme 2.86

2.3.5 Reactions with 1,3-Dipolar Compounds. Synthesis of Heterocyclic Systems

Phosphorus ylides react with 1,3-dipolar compounds containing a double carbon–nitrogen bond, e.g. azomethine oxides (nitrones), azometinimines, and azomethyneylides. These reactions proceed in high yields and lead to the formation of various heterocyclic compounds.

2.3.5.1 Reaction with Aziridines and Azomethine Ylides—Synthesis of Pyrrolines

Little information is available about the reaction of phosphorus ylides with simple aziridines. Heine and coworkers[170] found that reaction of triphenylphosphonium carboethoxymethylide with substituted aziridines leads to the formation of new C-alkylated ylides (Eq. 2.276):

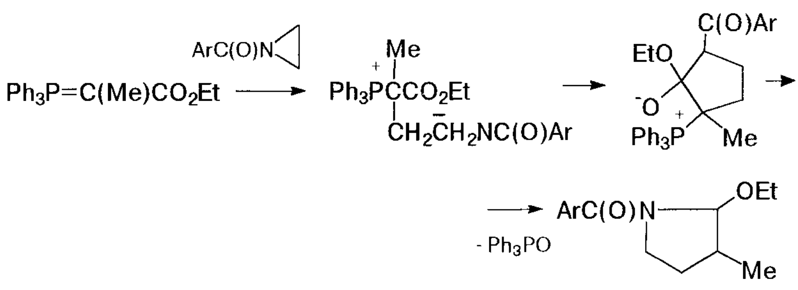


(2.276)

This is, however, a very rare example of C-alkylation of a phosphorus ylide with an azirine. Usually the reaction proceeds with the formation of heterocyclic systems, pyrroline and pyrrolidine derivatives. Thus when triphenylphosphonium carboethoxymethylide and 1-(*p*-nitrobenzoyl)aziridines are heated under reflux in toluene they react to afford 1-(*p*-nitrobenzoyl)-2-ethoxy-3-methyl-2-pyrrolidine, triphenylphosphine oxide and 2-*p*-nitrobenzoyl-2-oxazaline in low yield (Eq. 2.278)[170]:

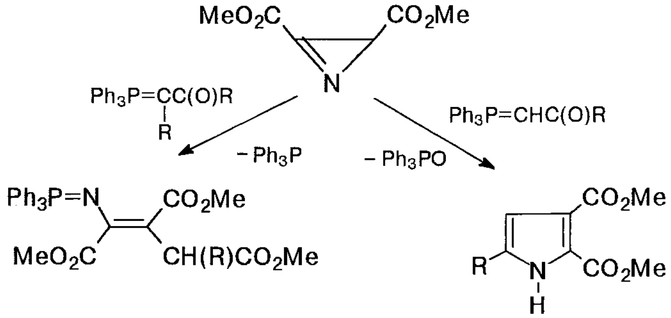
1-(p-Nitrobenzoyl)-2-ethoxy-3-methyl-2-pyrroline (Eq. 2.277)[170]

A mixture of triphenylphosphonium carboethoxymethylide (1.45 g) and 1-(*p*-nitrobenzoyl)aziridine (0.768 g) in dry toluene (70 mL) was heated under reflux for 6 h. The solvent was then removed under vacuum and absolute ether (3–4 mL) was added to the residue. The triphenylphosphine oxide was removed by filtration, the solvent was removed under reduced pressure, the residue was dissolved in a small quantity of dry benzene and purified by column chromatography (neutral aluminum oxide, benzene). The first 50 mL of the solution after evaporation provided 70 mg 2-*N*-nitrophenyl-2-oxazoline. The next fraction, 150–200 mL, furnished 360 mg pyrroline after evaporation; this was further purified by precipitation from DMFA with water; mp 142.5–145.5°C.



(2.277)

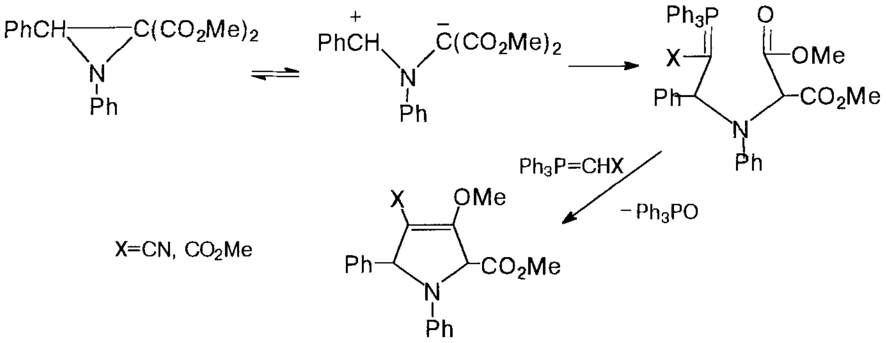
The reaction of 2,3-di(methoxycarbonyl)2-*H*-aziridine with keto- or ester-stabilized ylides leads to the formation of pyrroles or iminophosphonates (Scheme 2.87)[170,517,518]:



Scheme 2.87

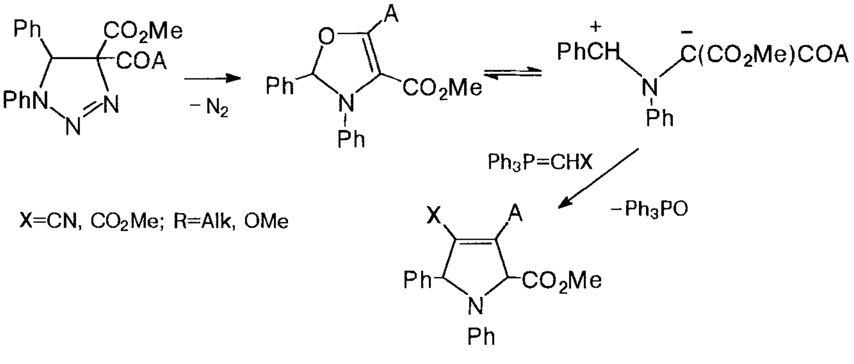
Photochemical irradiation of aziridines generates azomethyneylides; these are active 1,3-dipoles which readily undergo [3+2] cycloaddition reactions with different types of multiple bond. Azomethyneylides add smoothly to phosphorus ylides with the formation of nitrogen-containing heterocyclic compounds in good yields[519,520]. Triphenylphosphonium cyanomethylide and carbomethoxymethylide undergo nucleophilic addition to azomethyneylides generated from 2,3-dimethoxycarbonyl-1,3-

diphenylaziridine, to give isomers of pyroline-3 with a possessing different configuration of substituents on carbon atoms 1, 2, and 5. The ratio of isomers is 9:1 (X = CN) and 7.5:2.5 (X = CO_2Me), the yields are 70–90%. The reaction proceeds via the formation of a carbonyl-stabilized ylide which enters into an intramolecular Wittig reaction to afford the 3-pyrrolines after elimination of triphenylphosphine oxide (Scheme 2.88)[520a,520b,521]:



Scheme 2.88

Thermolysis of Δ^2-1,2,3-triazolines furnishes 2-oxazalines; these exist in equilibrium with azomethine ylides and the latter react in situ with phosphorus ylides to afford 3-pyrrolines (Scheme 2.89)[520]:

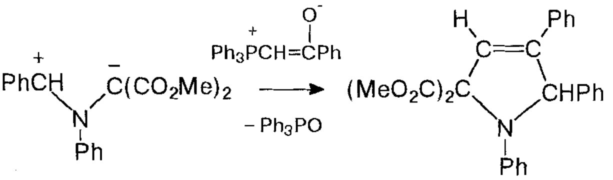


Scheme 2.89

The reaction of ylides (X = CN, CO_2Me) with 4-oxazalines (Scheme 2.89)[520]

4-Oxazoline was obtained by thermolysis of the triazoline. An equimolecular ratio (0.02 mol) of ylide and triazine was then heated under reflux in toluene (40 mL) under nitrogen. The reaction was monitored by NMR. When the reaction was complete, the solvent was removed under vacuum, and the residue was recrystallized from Et_2O–petroleum ether to separate the triphenylphosphine oxide. Fractional crystallization from alcohol furnishes the *cis* and *trans* isomers of pyrroline: X = CN, mp 192°C (*cis*), 206°C (*trans*), X = CO_2Me, mp 150°C (*cis*), 136°C (*trans*).

Azomethyneylides enter into 1,3-dipolar cycloaddition reactions with the C=C resonance bonds of triphenylphosphonium phenacylide with the formation of 3-pyrrolidines (Eq. 2.278)[522]:

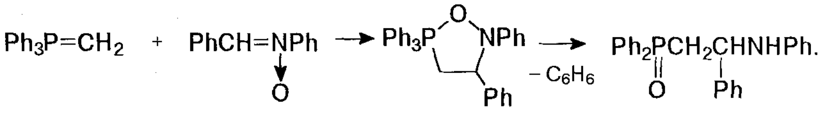


(2.278)

Hence P-ylides can, depending on structure, react with azomethyneylids as nucleophiles or 1,3-dipolarophiles

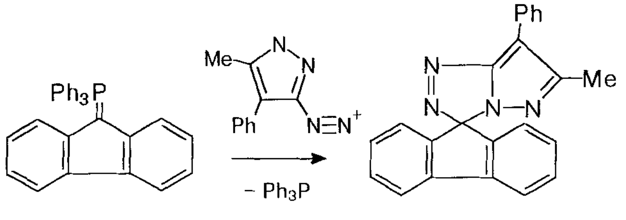
2.3.5.2 Oxides of Azomethines

Although phosphorus ylides behave like dipolarophiles toward N-oxides of azomethine ylides (nitrones), their activity the reactions with nitrones is not very high. Only active phosphorus ylides undergo reaction with these 1,3-dipoles to afford 1,2,5λ^5-oxaphospholanes. Thus, *C,N*-diphenylnitrone reacts with triphenyl-phosphonium methylide in ether at room temperature to afford crystalline (mp 135–136°C) 2,3,5,5,5-pentaphenyl-1,2,5λ^5--oxazaphospholidine in 93% yield. The chemical shift (d_P –58.6 ppm) of this compound corresponds to that of pentacoordinate phosphorus. Upon heating in xylene for 5 h the 1,2,5λ^5-oxazaphospholidine is converted into diphenyl (β-anilino-phenethyl) phosphine oxide (Eq. 2.279)[523,524]:



(2.279)

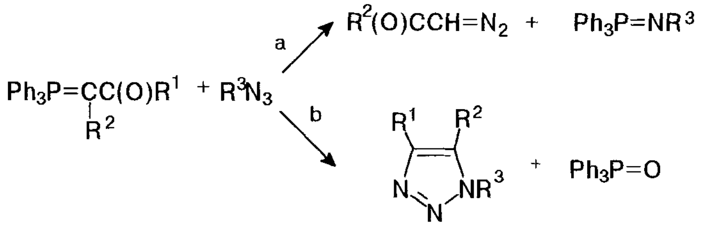
3,4-Dihydroisoquinoline oxide readily undergoes reaction with phosphorus ylides to affords tricyclic oxazaphospholidines in approximately 70% yield. Diazaalkanes are 1,3-dipoles, having octet stabilization and containing an orthogonal double bond. They react with phosphorus ylides at room temperature in benzene or toluene with the formation of azine and triphenylphosphine which reacts with excess diazaalkane to afford phosphazine. Diazapyrazoles undergo cycloaddition with triphenyl-phosphine fluorenylide to form 3*H*-*spiro*-pyrazolo(5-1*c*)[1,2,4]-pyrazole (Eq. 2.280)[525]:



(2.280)

2.3.5.3 Azides—Synthesis of 1,2,3-Triazoles

Organic azides function as 1,3-dipoles in reactions with phosphorus ylides. They react with phosphorus ylides to form 1,5-disubstituted 1,2,3-triazoles or diazacarbonyl compounds[526–539]. The reaction depends on the structure of the starting ylides and azides. For example, triphenylphosphonium carboethoxy-*methyl*ide reacts with azides at room temperature in dichloromethane to afford iminophosphoranes and diazo compounds in good yields (Scheme 2.90, route a, R′ = H) whereas that time triphenylphosphonium carboethoxy*ethyl*ide under the same reaction conditions furnishes 1-acyl-4-methyl-5-ethoxy-1,2,3-triazines (Scheme 2.90, route b, R′ = Me)[526–528]:



Scheme 2.90

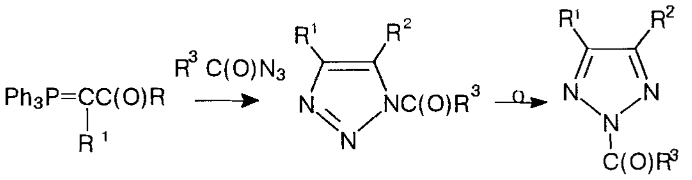
Reaction of triphenylphosphonium acylmethylides with azides is an convenient method for the preparation of *N*-1-substituted 1,2,3-triazoles in excellent yield (up to 98%, Table 2.19).[527,528,533] The reaction of *β*-keto-stabilized ylides with tosylazide can be applied for preparation of diazo compounds (Scheme 2.90). Thus *tert*-butyl diazoacetate was prepared in 63.5% yield after distillation in vacuo by reaction of triphenylphosphonium *tert*-butoxycarbonylmethylide with tosylazide (Scheme 2.90)[529]:

Synthesis of N-1-substituted 1,2,3-triazoles (General method, Scheme 2.90, Table 2.19)
A solution of azide (0.02 mol) in dichloromethane (20 mL) was added to a solution of triphenylphosphonium acylmethylide (0.02 mol) in the same solvent (50 mL). When the reaction was complete (0.25–80 h, checked by monitoring the IR azide stretching absorption at 2130 cm^{-1}) the solvent was evaporated and the residue was recrystallized from an appropriate solvent (methanol, ether, or benzene).

Preparation of 1-aryl-1,2,3-triazole (R^1 = Me, R^2 = Me, R^3 = 4-$O_2NC_6H_4$)[530]
The corresponding phosphorus ylide (R^1 = Me, R^2 = Me, 0.02 mol) was reacted with *p*-nitrophenylazide (0.02 mol) for 1.2 h at 80°C. The solvent was then removed by rotary

evaporation and the residue was recrystallized from MeOH or aqueous MeOH. Yield 73%, mp 139–140.5°C

Carbonylazides react with triphenylphosphonium acyl-stabilized ylides to afford *N*-2-acyl- and *N*-2-carboethoxy-1,2,3-triazoles as a result of the rearrangement of *N*-1-substituted triazoles forming during the first step of the reaction (Table 2.20). The *N*-1-substituted triazoles were monitored by NMR (Eq. 2.281)[534–536]:



(2.281)

Table 2.19. *N*-1-substituted 1,2,3-triazoles (Scheme 2.90)

R^1	R^2	R^3	Yield (%)	Ref.
H	Ph	$4\text{-}MeOC_6H_4$	81	534
H	Me	CO_2Et	98	532
H	Ph	Ts	65	528
H	Ph	Ph	80	530
H	Ph	CH=CHCOPh	95	538
Me	OEt	C(O)Ph	63	526
Me	OEt	CO_2Et	100	532
Me	Me	$C(Ph){=}CH_2$	54	538
H	Me	Ts	98	528
H	Ph	Ts	98	528
H	$4\text{-}O_2NC_6H_4$	Ts	87	528
H	Ph	$3,4\text{-}Cl_2C_6H_3CO$	97	528
H	$4\text{-}BrC_6H_4$	Ts	80	528
H	$4\text{-}BrC_6H_4$	Ph	24	528
H	Me	CO_2Et	65	532
$4\text{-}O_2NC_6H_4$	H	CO_2Et	40	532
EtO	Me	CO_2Et	100	532
Me	H	$4\text{-}O_2NC_6H_4$	73	530
Ph	H	Ph	80	530
$4\text{-}O_2NC_6H_4$	H	Ph	67	530
$4\text{-}O_2NC_6H_4$	H	$4\text{-}O_2NC_6H_4$	98	530

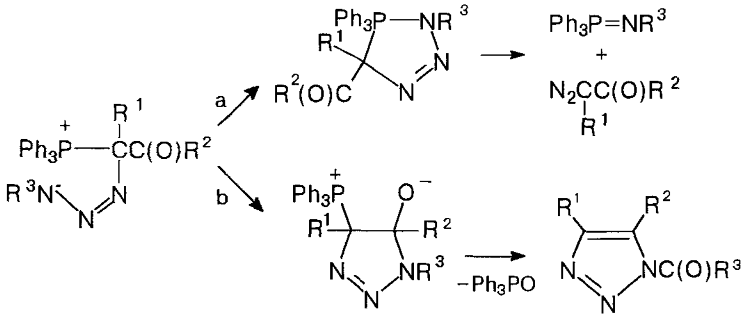
General method for the synthesis of N-2-substituted 1,2,3-triazoles (Eq. 2.283, Table 2.20)[536]

Equimolecular amounts (0.02 mol) of ylide and azide were reacted in dichloromethane or benzene (100 mL) at room temperature to completion (checked by monitoring the IR azide stretching absorption at 2130 cm^{-1}). Triazoles precipitated spontaneously from the dichloromethane solution or the solvent was removed and the residue was recrystallized from methanol, ether, or benzene

Table 2.20. *N*-2-substituted 1,2,3-triazoles (Eq. 2.281)

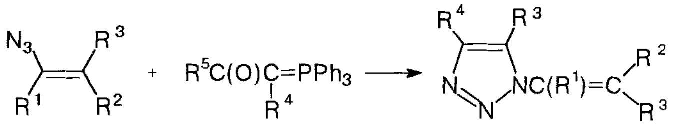
R^1	R^2	R^3	Yield (%)	Ref.
H	Me	Ph	50	530
H	Ph	Ph	49	530
H	Ph	4-ClC_6H_4	77	530
H	Ph	EtO	46	530
H	4-$O_2NC_6H_4$	EtO	76	530
H	Me	4-ClC_6H_4	79	530
Me	Me	3-$O_2NC_6H_4$	79	536
H	Me	4-$O_2NC_6H_4$	65	536
H	Ph	4-$MeOC_6H_4$	81	536
H	Me	4-$MeOC_6H_4$	23	536

Reaction of β-ketoylides with azides can proceed as concerted or stepped 1,3-dipolar cycloaddition depending on the nature of substituents R^1, R^2, R^3. In the first case concerted cycloaddition furnishes a five-membered cyclic phospho-rane, containing a P=C bond in the axial position; this decomposes with the formation of imidophosphorane and a diazo compound. In the second case the reaction proceeds with the formation of a betaine which readily eliminates triphenylphosphine oxide to afford 1,2,3-triazol (Scheme 2.91)[526,528]. Kinetic studies of the reaction of triphenylphosphonium β-ketoylides with azides showed that electron-accepting substituents R in the azide and electron-donating substituents R′ on the ylidic carbon atom increase the reaction rate. The activation entropy of the reaction is low, thus proving the concerted reaction mechanism[526,530–532]:



Scheme 2.91

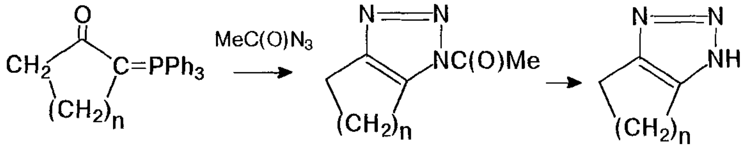
Reaction of triphenylphosphonium methylide with *o*-phthaloimidobenzoic acid azide leads to the formation of 1,5-disubstituted 1,2,3-triazoles, whereas β-ketoylides give linear phosphine azines[537]. The reaction of vinylazides with α-ketoylides furnishes 1-vinyl-1,2,3-triazoles; these were isolated in 20–98% yields (Eq. 2.282)[538]:



(2.283)

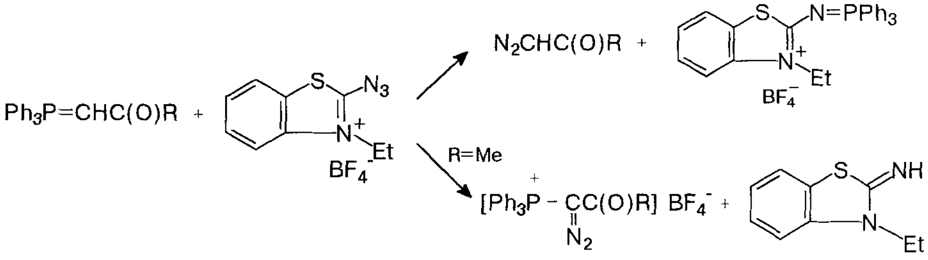
R^1=H, Ph, PhC(O); R^2=H, CN, PhC(O); R^2=H, Me, Ar; R^4=H, Me;
R^3=Me, Ph, 4-$O_2NC_6H_4$

Zbiral and coworkers[539] used the reaction of phosphorus ylides with acyl azides for the synthesis of various bicyclic triazoles (Eq. 2.283):



(2.284)

The reaction of triphenylphosphonium β-ketoylides with an equimolecular quantity of 2-azido-3-ethyl-1,3-benzothiazolium tetrafluoroborate in chloroform leads to the formation of α-diazacarbonyl compounds or 1-diazo-2-oxoalkylphosphonium salts (Scheme 2.92)[540,541]:

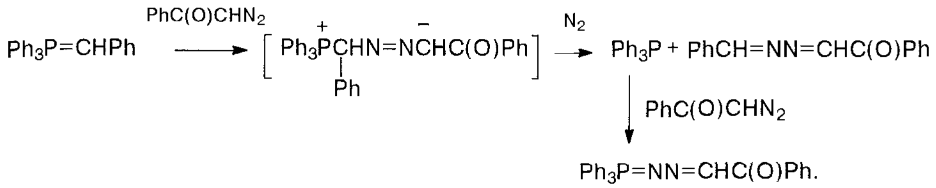


Scheme 2.92

Triphenylphosphonium benzylide reacts with an excess phenylazide to provide *N*-phenyliminotriphenylphosphorane and benzalaniline (Eq. 2.284)[542]:

$$\mathrm{Ph_3P{=}CHPh} \xrightarrow[-\mathrm{N_2}]{\mathrm{PhN_3}} \mathrm{PhCH{=}NPh} + \mathrm{Ph_3P} \xrightarrow[-\mathrm{N_2}]{\mathrm{PhN_3}} \mathrm{Ph_3P{=}NPh}. \qquad (2.285)$$

There have been few reports of the reaction of phosphorus ylides with diazo compounds[543,544]. This reaction usually furnishes products which retain the nitrogen. Maerkl[543] found that the reaction of triphenylphosphonium benzylide with diazoacetophenone results in a mixtures of azine and phosphinazine (Scheme 2.93):



Scheme 2.93

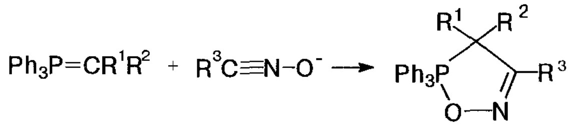
2.3.5.4 Reaction with Nitrile Oxides, Nitrilimines and Nitrilylides—Synthesis of Pyrazoles and Isoxazoles

Dipolar systems containing a carbon-nitrogen triple bond as a structural element include three important classes of compound—nitrile oxides, nitrilimines, and nitrilylides:

$$\overset{+}{R}C\equiv N-\overset{-}{O} \qquad RC\equiv\overset{+}{N}-\overset{-}{N}R \qquad RC\equiv\overset{+}{N}-\overset{-}{C}R_2$$

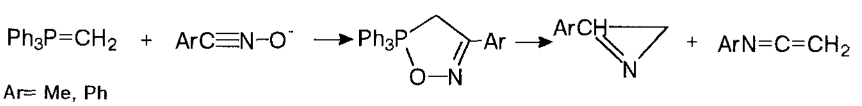
1,3-Dipoles containing carbon-nitrogen triple bonds readily undergo [3+2] cycloaddition to phosphorus ylides[544–556]. This reaction enables the preparation of various heterocyclic systems. Cycloadducts formed as a result of the addition of 1,3-dipoles to phosphorus ylides readily eliminate triphenylphosphine or triphenylphosphine oxide to produce heterocyclic or acyclic compounds.

Phosphorus ylides add to nitrile oxides to form 4,5-dihydro-1,2-oxaphosphalenes containing the pentacoordinate phosphorus atom; these have been isolated and characterized (Eq. 2.285)[545]:



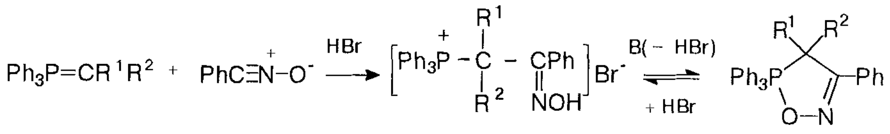
(2.285)

Wulff and Huisgen[546] found that benzonitrile oxide and triphenylphosphonium methylide react at room temperature to afford crystalline 3,5,5,5-tetraphenyl-4,5-dihydro-1,2,5λ^5-oxazaphosphole in 64–76% yield. Cyclo adducts prepared by reaction of benzonitrile oxide or mesitylenenitrile oxide with triphenylphospho-nium methylide upon heating in vacuo at 130–140°C eliminate triphenylphos-phine oxide to afford a mixture of 2-arylazirine and *N*-arylketenimine (Eq. 2.286)[546]:



(2.286)

The reaction of benzonitrile oxide with phosphorus ylides proceeds with the formation of 2-oximinophosphonium salts, which after treatment with bases result in cyclic oxaphospholenes (Eq. 2.287)[548]:



(2.287)

The oxime of 1-propylphenacyl triphenylphosphonium bromide (Eq. 2.287, R^1 = H, R^2 = Ph)[548]

(a) Preparation of solution of the triphenylphosphonium benzylide

A suspension of sodium hydride (50%, 3.2 g) was washed several times with hexane and mixed with dimethyl sulfoxide (distilled from calcium hydride, 150 mL). The mixture was then heated for 45 min at 75–80°C. After cooling to room temperature the solution of sodium dimsyl was added to benzyltriphenylphosphonium bromide (26 g) in THF (100 mL) with stirring and cooling with an ice bath.

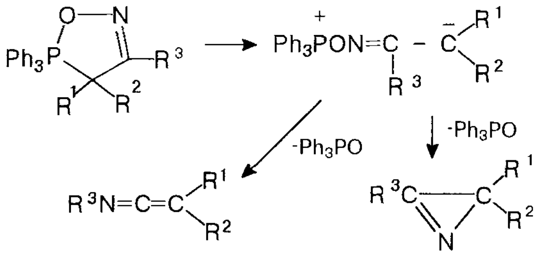
(b) Preparation of benzonitrile oxide solution

Triethylamine (9 mL) was added to a solution of the benzohydroxamic acid chloride (10 g) in absolute THF (50 mL) at −20°C. The precipitate of triethylamine hydrochloride was removed by filtration.

(c) The prepared solution of benzonitrile oxide was immediately added to the stirred solution of triphenylphosphonium benzylide at 0°C for 5 min. The mixture was left for 2 h at the room temperature and then poured into a mixture of a dilute solution of hydrobromic acid and crashed ice. The product was extracted with diethyl ether and the solution was left at room temperature to crystallize (~2 weeks). The salt (14.5 g, 45%) was removed by filtration. Recrystallization from ethanol–ether at 40°C gave the desired product, mp. 191°C (dec.).

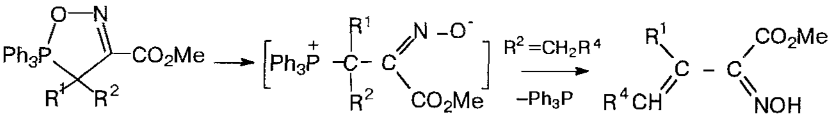
Cycloadducts of ylides and nitrile oxides are thermally unstable and upon heating undergo various transformations. These reactions depend on the electronic properties of groups R^1, R^2, and R^3 and their influence on the apicophilicity of substituents connected to the pentacoordinate phosphorus atom.

(a) If the P–C bond occupies an apical position it is cleaved when R^3 is alkyl or aryl, because of the pseudorotation of the substituents on the pentacoordinate phosphorus atom. A betaine is formed which eliminates triphenylphosphine oxide to produce azirine or ketenimine (Scheme 2.94)[549,550]:



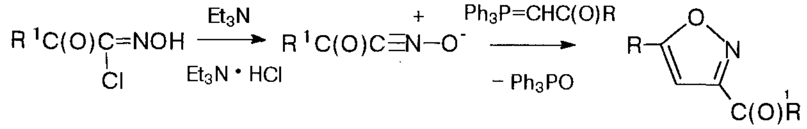
Scheme 2.94

(b) If the P–O bond occupies an apical position and R^3 is an electron-accepting group and R^1, R^2 are alkyl groups cleavage of the P–C bond leads to the formation of a betaine which eliminates triphenylphosphine. Intramolecular rearrangement results in α,β–unsaturated oximes (Eq. 2.288):

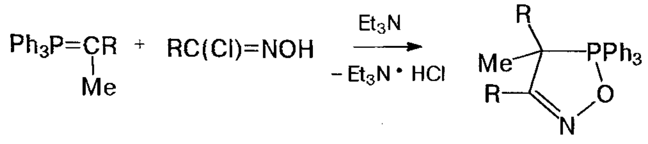


(2.288)

The reaction of 2 equiv. triphenylphosphonium β–ketoylides with *N*-oxohydroxamic acid chlorides affords acyl isoxazoles. In the presence of triethylamine, as an acceptor of hydrogen chloride, the reaction proceeds with 1:1 ratio of initial reagents (Eq. 2.290).[551] Oxazaphospholines have been obtained by reaction of C-alkyl-substituted β–ketoylides with *N*-oxohydroxamic acid chlorides (Eq. 2.291)[551]:



(2.289)



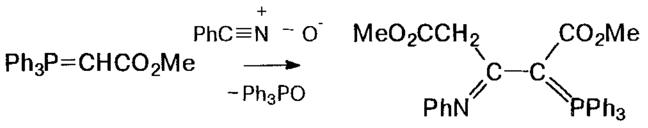
(2.290)

R=MeC(O)

4-Methyl-3,4-diacetyl-5,5,5-triphenyl-1,2,5-oxazaphosphole-2-yn (Eq. 2.290)[551]

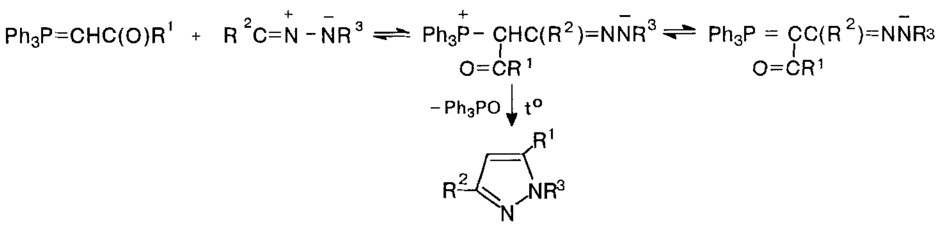
A solution of triphenylphosphonium 1-acetylmethylide (4 g) and triethylamine (1.2 g) in toluene (30 mL) was mixed with a solution of 4-chloroisonitrosoacetone (1.4 g) in of toluene (20 mL). The reaction mixture was left for 12 h and the triethylamine hydrochloride was removed by filtration, the solvent was removed under vacuum, and the residue was recrystallized from cyclohexane to furnish 3 g (60%) of the desired product, mp 83–84°C.

Benzonitrile oxide in benzene at 20°C reacts with 2 mol triphenylphosphonium carboethoxymethylide to afford a new ylide in 98% yield (Eq. 2.291)[546]:



(2.291)

The reaction of nitrilimines and nitrilylides with phosphorus ylides leads to the formation of five-membered heterocyclic systems[370,552–558]. On heating, as a result of cyclization and elimination of triphenylphosphine oxide, the betaines are converted into 3,5-disubstituted 1-arylpyrazoles (Scheme 2.95, Table 2.21)



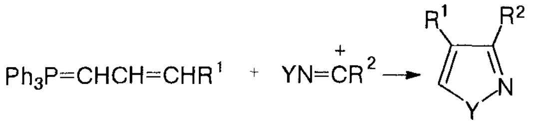
Scheme 2.95

Dalla Croce[555] studied the reaction of nitrilimines and nitrilylides with allylic ylides and obtained substituted pyrazoles and isoxazoles in good yields.

Table 2.21. Reaction of carbonyl-stabilized ylides with nitrilimines (Scheme 2.95)[370,492]

R^1	R^2	R^3	Yield (%)
Me	CO_2Me	Ph	70
OMe	CO_2Me	Ph	79
OMe	Ph	Ph	37
OEt	CO_2Et	Ph	86
OEt	COMe	Ph	71
OEt	CO_2Et	p-$O_2NC_6H_4$	80
NMe_2	CO_2Et	Ph	40
Ph	CO_2Et	Ph	79
CO_2Et	CO_2Et	Ph	20

This reaction was followed by [2+3] cycloaddition and by elimination of triphenylphosphine oxide. Triphenylphosphonium 3-cyano-3-formyl and 3-methoxycarbonylallylylides react with nitrile imides and nitrile oxides with the formation of the corresponding substituted pyrazoles and isoxazoles by elimination of a methyltriphenylphosphonium salt (Eq. 2.294, Table 2.22):



(2.294)

General procedure for the preparation of heterocyclic derivatives (Eq. 2.294)[555]
A mixture of the ylide (0.01 mol), the hydrazonyl halide or nitrile oxide (0.01 mol), and triethylamine (0.01 mol) in methanol (50 mL) was kept at room temperature for 2 h. The solvent was removed by evaporation and the residue taken up in benzene (75 mL) and water (25 mL). The heterocyclic compounds were obtained from the organic solution by conventional work-up.

Table 2.22 Pyrazoles and isoxazoles (Eq. 2.294)[555]

R^1	R^2	Y	Yield (%)
CN	CO_2Me	NPh	75
CO_2Me	CO_2Me	NPh	80
CO_2Me	Ph	NPh	75
CHO	Ph	NPh	60
CO_2Me	$C_6H_4NO_2$-4	O	64
CN	$C_6H_4NO_2$-4	O	70

So, C,P-carbon-containing phosphorus ylides have versatile reactivity and can be used as highly effective starting reagents for the synthesis of many important organic compounds. This synthetic versatility of the phosphorus ylides is shown most clearly by their reaction with carbonyl compounds (the Wittig reaction).

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Phosphorus Ylides: Chemistry and Application in Organic Synthesis
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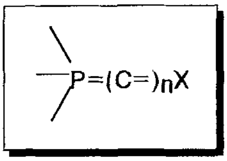
3 Cumulene Ylides

3.1 Introduction

Phosphacumulene ylides, phosphonium ylides with one or more double bonds cumulatively attached to the carbon atom of P=C[1-3], are clearly distinguished from other types of P-ylide by their structure and interesting chemical properties. Phosphacumulene ylides are:



$X=O, S, NR, CR_2; n \geq 1$

Several types of phosphacumulene ylides have been described: phosphaketene ylides **1**[1], phosphathioketene ylides, **2**[2], phosphaiminoketene ylides 3[3], phosphaketene-acetal ylides **4**[4], phosphathioketeneacetal ylides **5**[5], phosphaallene ylides **6**[6], and phosphacumulene ylides **7**[7] (Scheme 3.1). In 1966 Matthews and Birum synthesized the first phosphacumulene ylides by reaction of hexaphenylcarbodiphosphorane with heterocumulenes[4-6]. They prepared the first triphenylphosphonium ketene ylide **1**, thioketene ylide **2**, and iminoketene ylides **3** (Scheme 3.1). Matthews also obtained the first phosphaallene ylides **8** by reaction of hexaphenylcarbodiphosphorane with hexafluoroacetone[7].

$Ph_3P=C=C=O$ **1**
$Ph_3P=C=C=S$ **2**
$Ph_3P=C=C=NR$ **3**
$R_3P=C=C(OR)_2$ **4**
$R_3P=C=C=C(SR)_2$ **5**
$R_3P=(C=)_nCR'_2$ **6** (n=1), **7** (n=2)
$Ph_3P=C=C(CF_3)_2$ **8**
$Ph_3P=C=C=CPh_2$ **9**
$Ph_3P=C=C(OEt)_2$ **10**

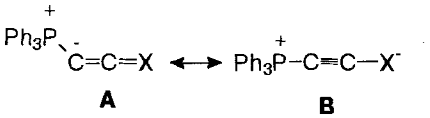
Scheme 3.1

Later Ratts and Partos[8] synthesized phosphacumulene ylide **9** and Bestmann and co-workers, who made the most important contribution to the chemistry of phosphacumulene ylides[1,3], synthesized phosphaketeneacetal ylide **10**[9].

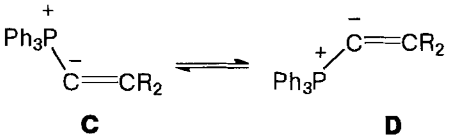
3.1.1 The Structure of Phosphacumulene Ylides

The molecular structure of phosphacumulenes has been studied by X-ray crystallography, which showed that the hybridization of the *a* carbon atom was close to sp^2 (Eq. 3.1)[10–14].

X-ray crystallographic analysis of several triphenylphosphonium phosphacumulene ylides showed that P–C–C angles are, on average 125.6–145.5° and the C=C bond lengths are very close to the C≡C bond length. The P–C–C angles of ylides are increased, and the lengths of the P=C bonds correspond to the C≡C bond length, indicating that the resonance structure with the triple C≡C bond predominates in ground state of phosphacumulene ylides [12]. The fast inversion C ⇌ D of phosphaallene ylides has been observed at –70 °C by NMR (Eq. 3.2)[15].

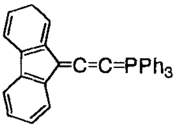


(3.1)



(3.2)

Table 3.1. The P=C bond lengths and the P=C=C bond angles of phosphacumulene ylides and phosphaallene ylides

Compound	Ylides	d(P=C) Å	d(Ca-Cb) Å	<PCC°	Ref
1	$Ph_3P{=}C{=}C{=}O$	1.648	1.210	145.5	10
2	$Ph_3P{=}C{=}C{=}S$	1.677	1.209	168.0	13
3	$Ph_3P{=}C{=}C{=}NPh$	1.677	1.248	134.0	11
10	$Ph_3P{=}C{=}C{=}C(OEt)_2$	1.682	1.314	125.6	12
11		1.703	1.243	136.5	14

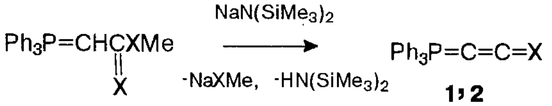
3.2 Phosphaketene Ylides

Accessible methods have been developed for the synthesis of phosphaketene ylides. The most simple method for the preparation of phosphaketene ylides, thioketene ylides, iminoketene ylides is the reaction of the phosphonium methylides with phosgene, thiophosgene or N-substituted iminophosgene. The reaction proceeds with a 3:1 ratio of starting reagents, resulting in cumulene ylides which are isolated and purified by crystallization. The yields of ylides were 60–70% (Eq. 3.3, Table 3.2, method A)[16,17]:

$$3Ph_3P{=}CH_2 \xrightarrow[-2[Ph_3\overset{+}{P}Me]Cl^-]{Cl_2C{=}X} \underset{\mathbf{1-3}}{Ph_3P{=}C{=}C{=}X} \qquad (3.3)$$

X = O, S, NR;

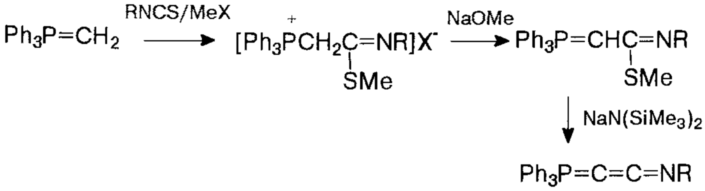
A convenient method for the preparation of the phosphaketene ylide **1** is reaction of triphenylphosphonium carboalkoxymethylides with sodium bis(trimethylsilyl)amide[18] or phenyllithium.[20] The reaction proceeds in benzene with the *β*-elimination of methanol to furnish the ketene ylide **1** in 80% yield. Under analogous conditions the thioketene ylide **2** was prepared from triphenylphosphonium carbothioalkoxymethylide in 76% yield (method B, Eq. 3.4, Table 3.2,).[18–22,24]



$$Ph_3P{=}CH\underset{\overset{\|}{X}}{C}XMe \xrightarrow[-NaXMe,\ -HN(SiMe_3)_2]{NaN(SiMe_3)_2} \underset{\mathbf{1, 2}}{Ph_3P{=}C{=}C{=}X} \qquad (3.4)$$

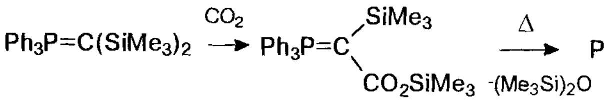
X=O, S

Bestmann proposed an improved method for the synthesis of triphenylphosphonium keteneimino ylide (Scheme 3.2)[23].



Scheme 3.2

The convenient method for the synthesis of the phosphaketene ylide **1** serves also for reaction of the bis(trimethylsilyl)substituted ylide with the carbon dioxide.[25] The reaction affords firstly trimethylsilylacyl ylides, the thermolysis of which furnishes triphenylphosphonium ketene ylide **1** (Method D, Eq. 3.5, Table 3.2).



$$Ph_3P{=}C(SiMe_3)_2 \xrightarrow{CO_2} Ph_3P{=}C(SiMe_3)(CO_2SiMe_3) \xrightarrow[-(Me_3Si)_2O]{\Delta} Ph_3P{=}C{=}C{=}O \qquad (3.5)$$

1

Table 3.2. Phosphaketene ylides $Ph_3P{=}C{=}C{=}X$

X	mp	Method	Yield, (%)	δ_P, ppm	IR, cm^{-1}	Ref
O	171-172°C[a)]	B	80	5.37	2080	20,22,24
O		D				35
S	223-226	A	60	-8.02	1965, 2110	16,17
S	224-226[b)]	B	76	-8.17	1965, 2110	22,24
NMe	157-158	A	70	6.18	1980	16,21
NMe	161	C	71	6.24	1980	23
NPr	141	C	69	8.17.	1990	23
NPh	151-152	A	85	2.30	2000	16,21
NPh	153	C	85	2.39	2000	23
NC_6H_4Cl-4	183	A	75	3.12	1995	16,21
$NC_6H_3Cl_2$-(2,4)	183	A	75	3.45	1990	16,21
NC_6H_4Me-4	89-91	A	69	2,71	2000	16,21

3.2.1 Chemical Properties

Phosphaketene ylides **1–3** are highly unsaturated compounds. They undergo readily the addition and cycloaddition reactions. In contrast to organic ketenes the Phosphaketene ylides have nucleophilic properties only, in accordance with the presence of the additional electron pair on the ylidic carbon atom and two orthogonal π-electron orbitals (Eq. 3.6)[1,4]:

$$Ph_3\overset{+}{P}-\overset{-}{C}=C=O \longleftrightarrow Ph_3\overset{+}{P}-C\equiv C-O^- \qquad (3.6)$$

$$R_2\overset{-}{C}-C\equiv O^+ \longleftrightarrow R_2C=C=O \longleftrightarrow R_2\overset{+}{C}=C-O^- \qquad (3.7)$$

Conversely, organic ketenes are biphilic compounds because of the presence of two reaction centers—nucleophilic on the β carbon atom and electrophilic on the α carbon atom (Eq. 3.7)[26].

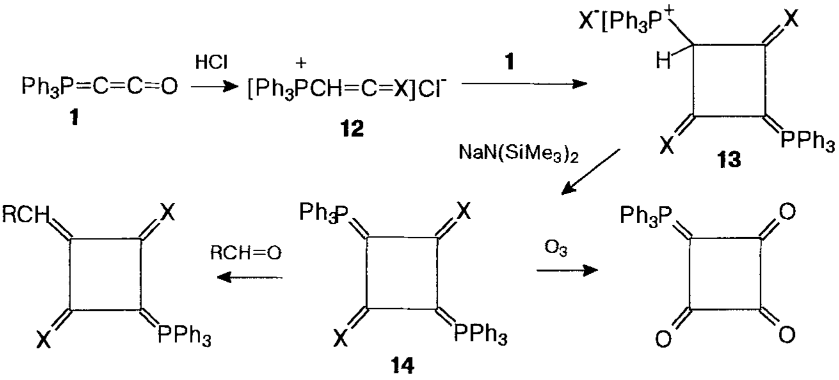
The C=C bond of phosphacumulenes undergoes a wide variety of addition reactions; unlike organic ketenes, however, the phosphaketene ylides and their analogs do not form dimers under normal conditions

3.2.2 Dimerization

Phosphaheterocumulene ylides **1–3** are stable compounds, which can be stored in a closed vessel for a long time without dimerization.

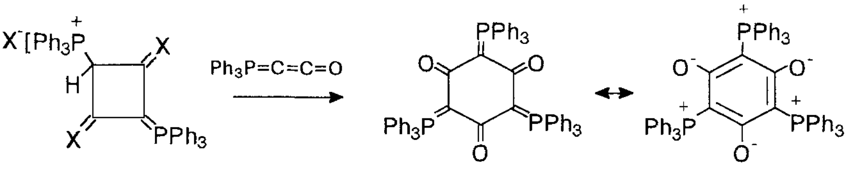
Treatment of the phosphaketene ylide **1** with HCl initially furnishes the ketenylphosphonium salt **12** which immediately undergoes a cycloaddition reaction with another molecule of ylide **1** to give the salt **13**[27,28].

Deprotonation of the phosphonium salts **13** with sodium bis(trimethylsilyl)amide affords cyclic bis-ylides **14**—the dimers of starting ketenylides[27]. Bis-ylides **14** are highly reactive compounds. They readily undergo the Wittig reaction with aldehydes to form cyclic monoylides. Oxidation of **14** with ozone or with *N*-*p*-tolylsulfonyl (phenyl)oxaziridine leads to the formation of the squaric acid ylides (Scheme 3.3): [28]



Scheme 3.3

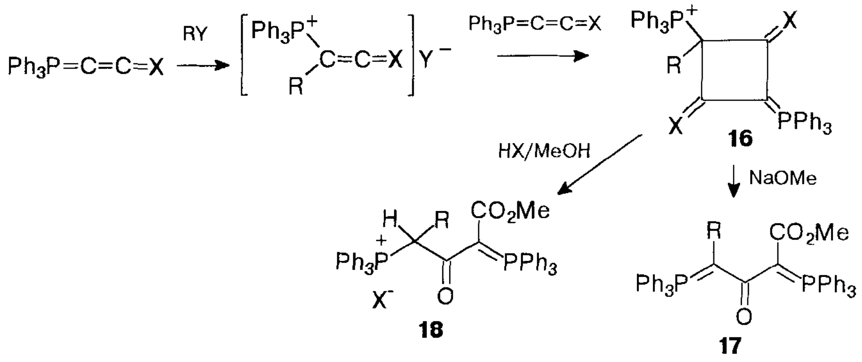
Trimers of ketene ylides **15** have been prepared by reaction of the cyclic phosphonium salt **13** with phosphacumulene ylide (Eq. 3.8)[29]. The salt **13** was heated under reflux with an eightfold excess of ketene ylide **1** in dichloromethane for 16 h to produce yellow crystals of the desired trimer in 30% yield. According to X-ray crystallography the central six-membered ring of **15** is not planar but has a twisted-boat conformation. Evidently the trimer **15** is a hybrid between an arene and an ylide[28]:



(3.8)

13 **15**

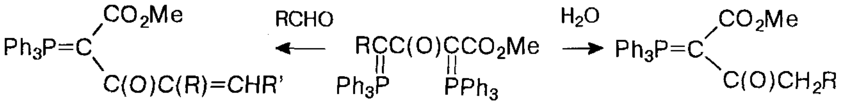
Phosphaketene ylide **1** with high nucleophilicity, readily react with alkyl halides. Reaction proceeds via the formation of ketene phosphonium salts with dipolar properties which undergo [2+2]-cycloaddition with the starting phosphaketene ylides to produce 1,3-cyclobutandionylide phosphonium salts **16**. These salts were isolated as stable crystalline solids in yields of 87–96% (Scheme 3.4)[1,30,32]. Ring opening of **16** under different conditions gives rise to bis-ylides, **17**, ylide salts, **18**, and other products[21]. Reaction of triphenylphosphonium ketene ylide **1** with 0.5 equiv. bromine (R = Br) proceeds analogously. The yield of the cyclic ylide phosphonium salt (**16**, X = O) after purification was 96%.



X=O, NPh; R=Me, Et, C_5H_{11}, $PhCH_2$, α-$C_{10}H_7CH_2$; Y=Br,I

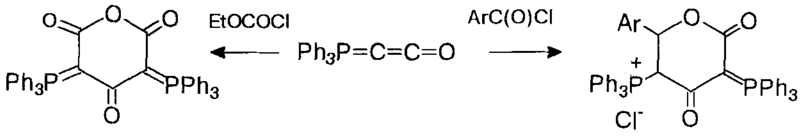
Scheme 3.4

The hydrolysis and the Wittig reaction of the bis-ylides **17** proceed selectively at the one P=C group with the formation of stable dicarbonyl-substituted phosphorus ylides **18** and **19**. The yields of ylides are on average 80–85% (Eq. 3.9)[30,32,34]:



$$\underset{\mathbf{18}}{Ph_3P{=}C\begin{smallmatrix}CO_2Me\\ C(O)C(R){=}CHR'\end{smallmatrix}} \xleftarrow{RCHO} \underset{\mathbf{17}}{R\underset{Ph_3P}{\overset{}{C}}C(O)\underset{PPh_3}{C}CO_2Me} \xrightarrow{H_2O} \underset{\mathbf{19}}{Ph_3P{=}C\begin{smallmatrix}CO_2Me\\ C(O)CH_2R\end{smallmatrix}} \qquad (3.9)$$

Phosphaketene ylide **1** reacts with aromatic acyl chlorides to give pyrone derivatives in high yields. Reaction of **1** with ethyl chloroformate results in pyrilium betaine (Eq. 3.10)[32]:



(3.10)

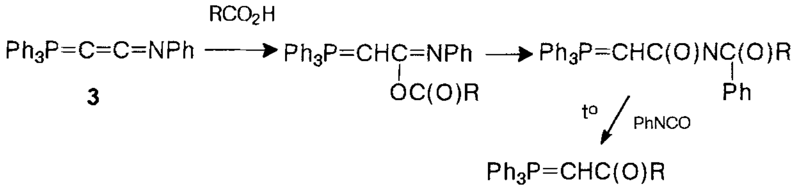
3.2.3 Addition of Compounds Bearing a Mobile Hydrogen Atom

Phosphacumulene ylides **1**–**3** add compounds bearing a mobile hydrogen atom, producing the phosphorus ylides, **21**, stabilized by a C=X group[4]. The reaction proceeds via the formation of an ion-pair **20** containing a nucleophilic anion (Eq. 3.11)[35–40]. The addition of alcohols, thiols, phenols, sulfo- and carboxylic acid amides, nitrogen-containing heterocyclic compounds (acyl imidazoles and pyrazole), CH-acids (malonodinitrile, 1,3-dicarbonyl compounds, and others) to phospha-cumulene ylides (X= O, S, NR) results in C-acyl-substituted phosphorus ylides **21** in 53–83% yields[35,39]:

$$\underset{\mathbf{1\text{-}3}}{Ph_3P{=}C{=}C{=}X} + HY \longrightarrow \underset{\mathbf{20}}{[Ph_3PCH{=}C{=}X]^+Y^-} \longrightarrow \underset{\mathbf{21}}{Ph_3P{=}CHC(X)Y} \qquad (3.11)$$

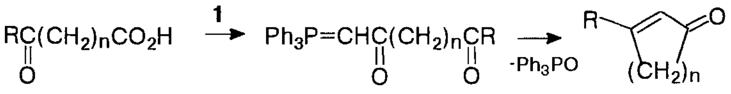
$Y= ROH,\ AlkSH,\ ArSH,\ PhSO_2NH_2,\ CH_2X_2,\ HNX$

Triphenylphosphonium *N*-phenylketeneimine **3** ylide adds carboxylic acids to afford ylides which when heated eliminate phenyl isocyanate to give rise to acyl ylides (Scheme 3.5)[32,35]:

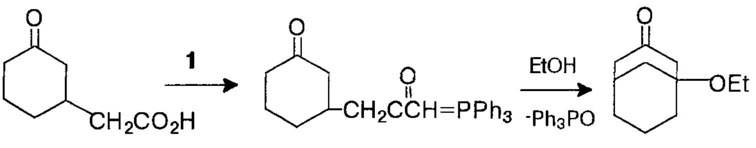


Scheme 3.5

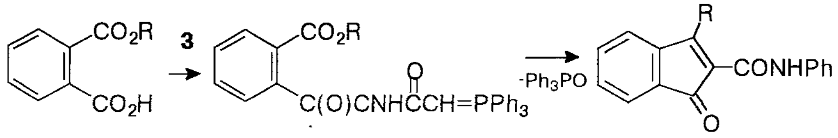
Acyl ylides, generated from *ω*-ketocarboxylic acids and ketene ylide **1**, enter into the intramolecular Wittig reaction with the formation of cycloalkenones (Eq. 3.12). Bestmann and co-workers used this reaction for the preparation of carbocycles (Eq. 3.13,14)[36,54]:



(3.12)

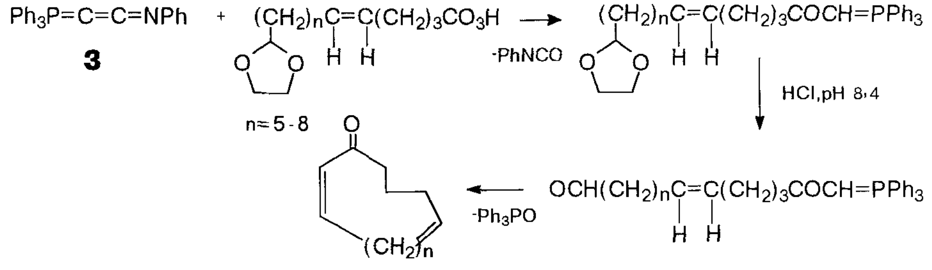


(3.13)



(3.14)

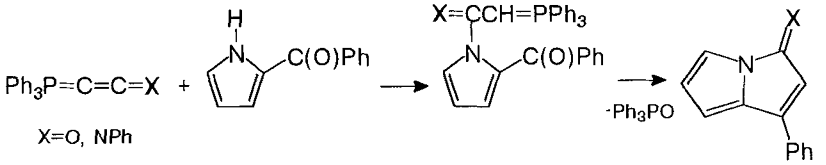
Reaction of *N*-phenylketeneimine ylide **3** with carboxylic acids has been applied to the synthesis of macrocyclic ketones **22** (Scheme 3.6)[44]:



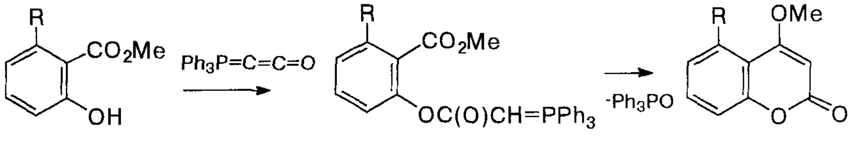
22

Scheme 3.6

Phosphaketene ylides, are initial reagents for the preparation of heterocyclic compounds. Addition of aldehydes or ketones to phosphaketene ylides containing OH, SH, or NH groups results in phosphorus ylides which undergo an intramolecular Wittig reaction to furnish a number of heterocyclic compounds (Eq. 3.15,16)[42–49]:



(3.15)



(3.16)

1-Phenyl-3H-pyrrolidine-3-one[38] (Eq. 3.15, X = O)

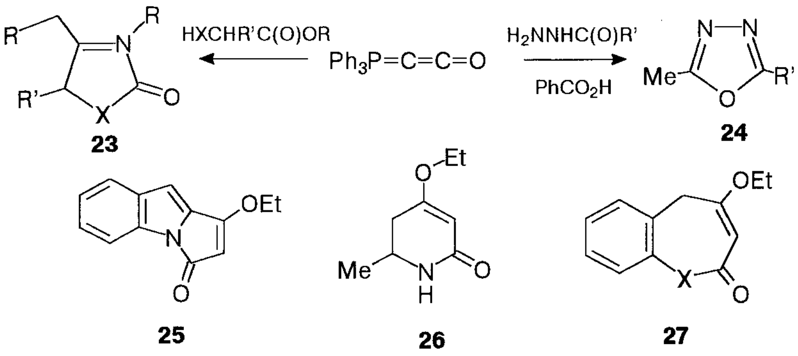
Triphenylphosphonium ketene ylide (3.02 g, 10 mmol) was mixed with 2-benzoylpyrrole (1.71 g, 1.0 mmol) and absolute benzene (100 mL) and the reaction mixture was heated under reflux for 12 h. The solvent was removed under vacuum and the residue was chromatographed over silica gel with benzene as an eluent. Yield 86%, mp 81°C.

1,1-Diphenyl-3H-pyrrolidine-3-imine (Eq. 3.15, X = NPh)

A solution of *N*-phenyl triphenylphosphonium ketene ylide (3.77 g, 10 mmol) and 2-benzopyrrole (1.71 g, 10 mmol) in benzene (60 mL) was heated under reflux for 12 h. The solvent was then evaporated and the residue was chromatographed over silica gel with benzene or crystallized first from methanol and then from toluene. Yield 2.19 g (81%), mp 99°C.

A new route to five-, six- and seven-membered O-, N-, and S-heterocyclic compounds **23–27** via intermolecular Wittig olefination of hydrazide and α-, β-, and γ-substituted carboxylic esters with ketenylidene was developed by Loeffler and Schobert (Scheme

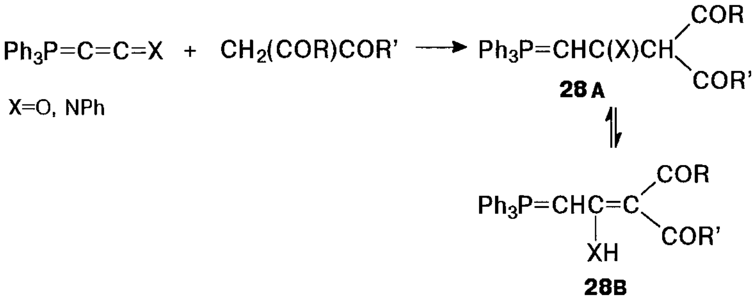
3.7)[42,43]. α-Hydroxyamides react with the ketene ylide to give 2(3*H*)-oxazolones via an addition–cyclization–intermolecular Wittig olefination sequence:



X=O, S, NH

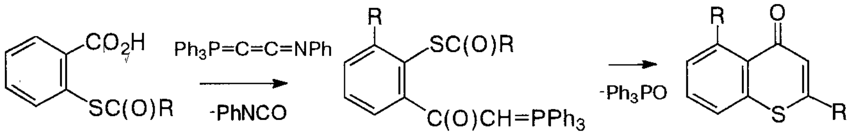
Scheme 3.7

Phosphaketene ylides and phosphaketeneimine ylides add 1,3-dicarbonyl compounds with the formation of phosphorus ylides, which exist in tautomeric equilibrium **28A** $\rightleftharpoons$ **28B** (Scheme 3.8)[19]:



Scheme 3.8

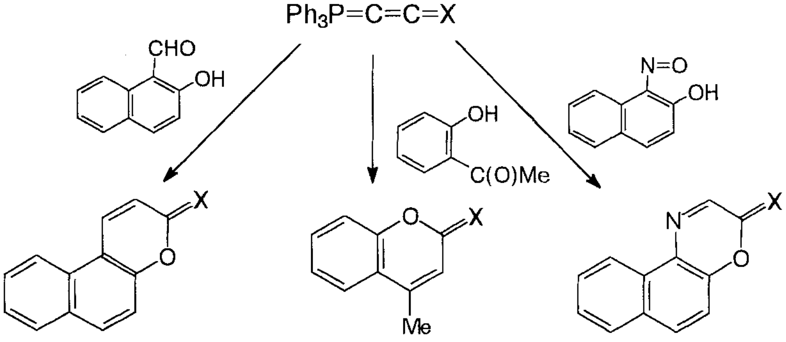
The reaction of *S*-acyl(aroyl)thiosalicylic acids with *N*-phenylketeneimine ylide in stepwise fashion leads to acyl ylides which subsequently undergo intramolecular Wittig cyclization on the thiol ester carbonyl to afford 4*H*-1-benzothiopyran-4-ones in high yield (Eq. 3.17)[38,52]:



29

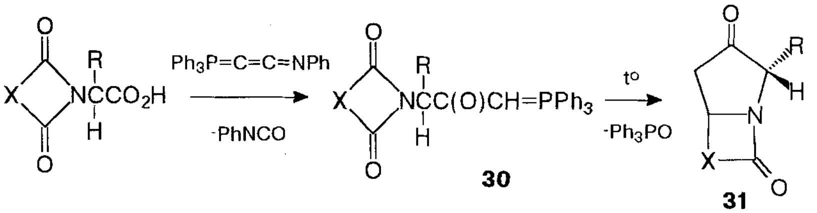
(3.17)

The reaction of phosphacumulene ylides with arylketones and arylaldehydes bearing an OH or XH group and some nitroso compounds proceeds analogously[38,52,53]. Examples of such reactions are shown in Scheme 3.9.



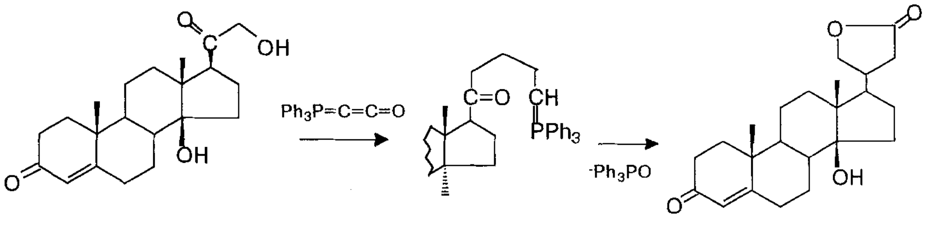
Scheme 3.9

Cyclic *N,N*-diacyl amino acids have been converted to pyrrolizidenediones by reaction with *N*-phenylketene ylide (Eq. 3.18). When heated under reflux in ethyl acetate the reaction proceeds with elimination of phenyl isocyanate to result in pyrrolizidinediones via intramolecular Wittig reaction. The acyl ylides **30** were isolated and converted into pyrrolizidenediones **31**[50]:



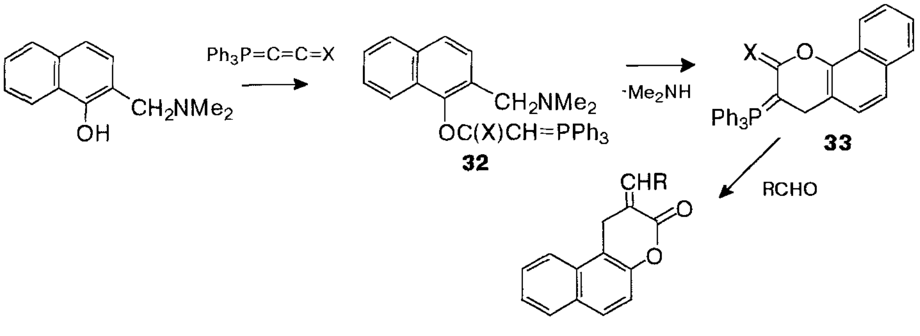
(3.18)

The reaction of triphenylphosphonium ketene ylide with steroids bearing an hydroxyketone group on a side-chain, furnishes cardenolides with butenolide ring in high yields (Scheme 3.10). [51]



Scheme 3.10

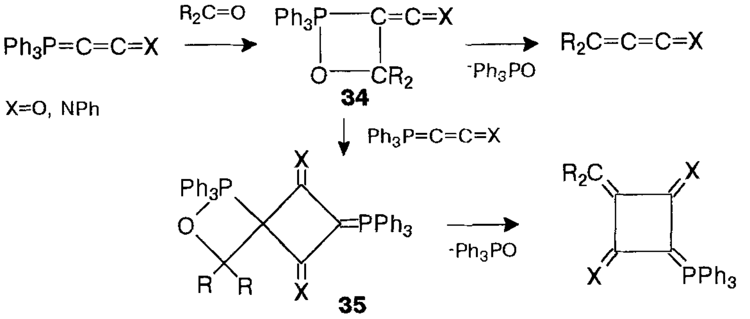
Phosphaketene ylides react with phenols bearing dialkylaminomethyl groups to afford ylides **32** which undergo intramolecular cyclization to produce cyclic phosphorus ylides **33**. The latter compounds are starting reactants for the synthesis of heterocyclic compounds (Scheme 3.11)[38,54]:



Scheme 3.11

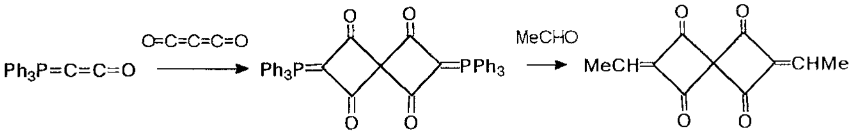
3.2.4 [2+2] Cycloaddition Reactions

The reaction of phosphorus ketene ylides with aldehydes and ketones leads to the formation of a [2+2]-cycloadduct **34** which eliminates triphenylphosphine oxide to produce an alkylideneketene (alkylideneimine, X = NPh) or reacts with a second molecule of starting phosphaketeneimine to afford spiro compounds **35**. Elimination of the triphenylphosphine oxide from the spiro compounds results in phosphonium cyclobutanedione ylides which can be isolated as crystalline substances in yields of 50–70% (Scheme 3.12)[31]:



Scheme 3.12

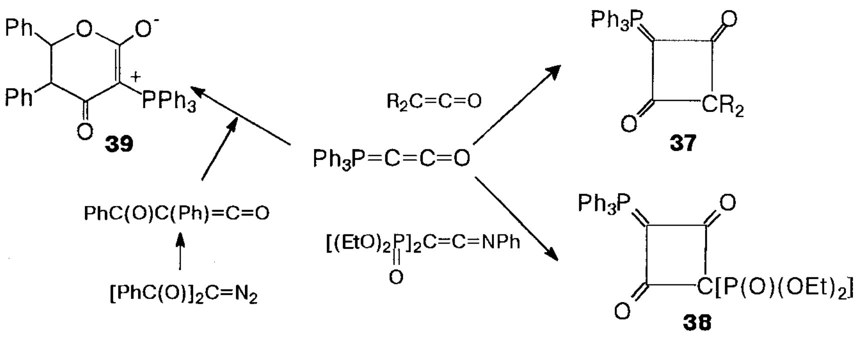
Pandolfo and co-workers recently reported the reaction of ketene ylide with the simplest stable bis-ketene, carbon suboxide, leading to the formation of *spiro*-bis(cyclobutenedione) **36**. The latter underwent a Wittig reaction (Eq. 3.19)[55]:



(3.19)

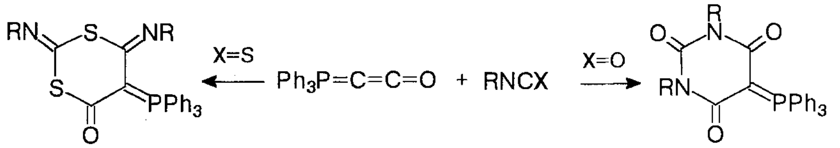
36

Phosphaketene ylides undergo [2+2]-cycloaddition reaction with ketenes and keteneimines to afford phosphonium cyclobutanedione ylides **37**,**38**. The reaction of acyl ketenes with phosphaketene ylides proceeds with the formation of γ-pyrrone derivatives **39** (Scheme 3.13)[56]:



Scheme 3.13

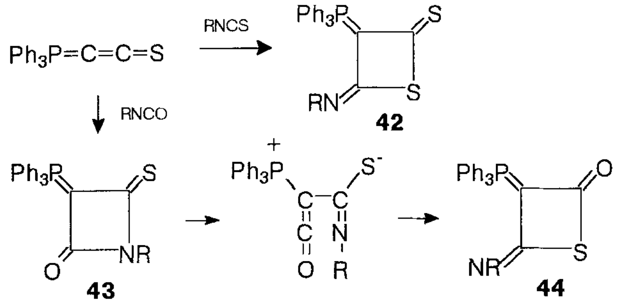
The reaction of isocyanates with phosphaketene ylides proceeds with the formation of pyrimidine phosphonium ylides **40** [1,31]. Isothiocyanates react with phosphaketenes in a 2:1 ratio to result in dithio derivatives **41** (Scheme 3.14)[56]:



41 **40**

Scheme 3.14

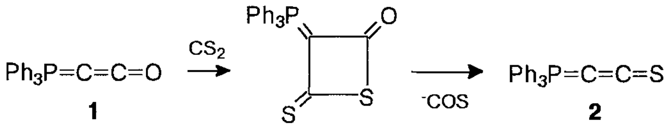
Phosphathioketene ylides undergo [2+2]-cycloaddition with isothiocyanates to afford cyclic phosphorus ylides **42** as a result of addition of the C=C bond to the C=S bond[56,57] At the same time the addition of isocyanates to phosphathioketenes affords cyclic phosphorus ylides **44** bearing exocyclic C=O and C=S groups. [2+2]-Cycloaddition of: the thioketene ylide C=C bond to the isocyanate C=O bond probably produces a cyclo adduct **43** which via ring opening and subsequent retrocyclization is converted into the



Scheme 3.15

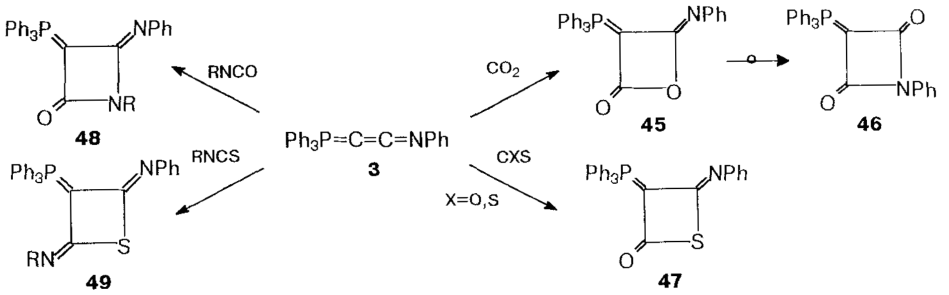
final reaction product. Heterocyclic compounds with an exocyclic iminomethylene group are probably energetically more stable than heterocyclic compounds with a thione group (Scheme 3.15)^{56,57}:

Reaction of phosphaketene ylide **1** with carbon disulfide results in triphenylphosphonium thioketene ylide **2**. The primary product of addition is four-membered cyclic ylide which eliminates COS to produce thioketene ylide **2** (Eq. 3.20)^{33b}:



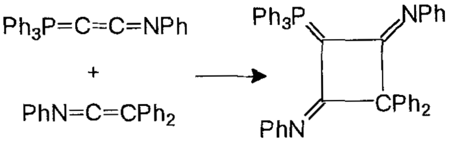
(3.20)

Triphenylphosphonium *N*-phenylketeneimine ylide reacts with carbon dioxide to afford triphenylphosphonium *N*-phenylmalonoimido ylide **46** (Scheme 3.16). . The reaction proceeds via the formation of an initial addition product to the C=O bond **45**, which then rearranges into ylide **46.**^{1,58} Reaction of phosphaketeneimino ylide with COS and CS$_2$ occurs at the C=S bond to result in the [2+2]-cycloaddition product **47**^{58}. Analogously the reaction of keteneimino ylide **3** with isocyanates results in a cyclic ylide **48** bearing exocyclic C=O and C=N groups, and reaction with isothiocyanates leads to the formation of the four-membered cyclic P-ylide **49**^{56,57}:



Scheme 3.16

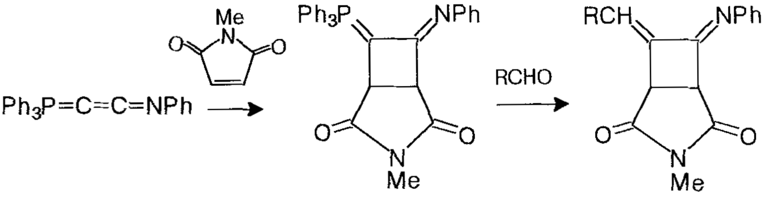
N-Phenyliminodiphenylketene reacts with triphenylphosphonium *N*-phenylketeneimine ylide to afford the [2+2]-cycloaddition product **50** (Eq. 3.21)[1]:



50

(3.21)

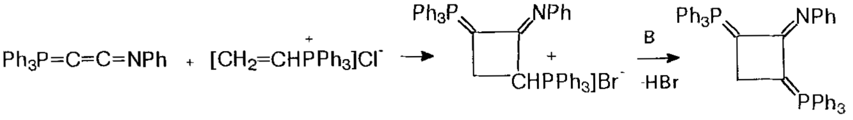
Keteneimino ylides with high nucleophilicity can react with electron-deficient C=C double bonds, in contrast with organic ketenes and keteneimines which readily add to electron-enriched C=C bonds. Triphenylphosphonium *N*-phenyl-keteneimine ylide undergoes [2+2]-cycloaddition with *N*-methylmaleinimide to result in *N*-phenyliminocyclobutanylide, **51**. Wittig reaction of the compound **51** with aldehydes furnishes the bicyclic derivative **52** (Eq. 3.22)[3,57]:



51 **52**

(3.22)

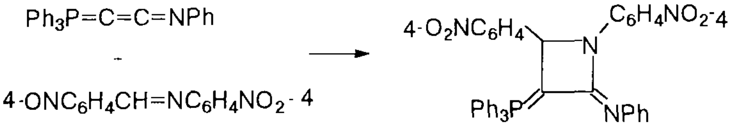
Keteneiminoylide reacts with vinylphosphonium salts to form four-membered cyclic ylide phosphonium salts **53**, deprotonation of which furnishes bis-ylides **54** (Eq. 3.23)[1]:



53 **54**

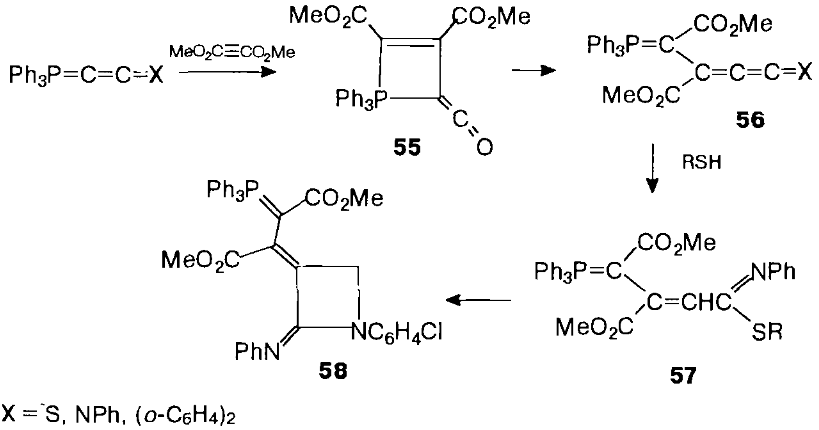
(3.23)

Bestmann reported a single example of a reaction between an activated Schiff base, *N*-(*p*-nitrobenzylidene)-*p*-nitroaniline, and triphenylphosphonium *N*-phenylketeneimino-ylide (Eq. 3.24)[1]:



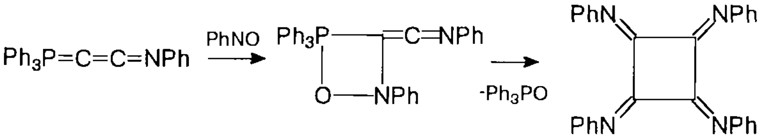
(3.24)

Phosphacumulene ylides add dimethylacetylenedicarboxylate to result in the acyclic ylide **56** (Scheme 3.17).[16,59,60] Phosphorus ylide **56** adds ethane thiol to furnish the new conjugated ylide **57**, which readily enters into a [2+2]-cycloaddition reaction with 3,4-dichlorphenylisocyanate to result in the ylide **58** (Scheme 3.17).



Scheme 3.17

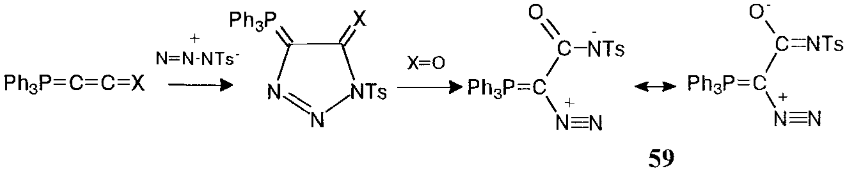
The reaction of *N*-phenylketeneimine with nitrosoaniline resulting in a dimer of bis-cumuleneimine has also been described (Eq. 3.25)[61].



(3.25)

3.2.5 1,3-Dipolar Addition Reactions

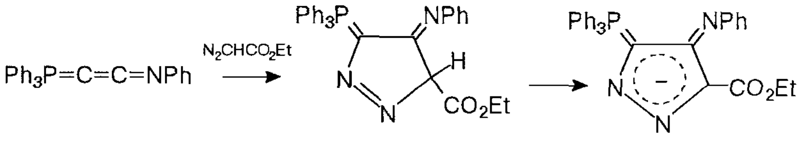
Phosphacumulene ylides enter into a 1,3-dipolar cycloaddition reaction with toluenesulfonyl azide to afford the phosphonium triazolylide. The five-membered ring of the triazolylide containing X = O readily opens producing a phosphorus ylide **59** bearing a diazo group (Eq. 3.26)[1]. The IR spectrum of the compound **59** contains the absorption band of the diazo group at 2150 cm^{-1}:



59

(3.26)

Diazoacetic ester reacts with triphenylphosphonium *N*-phenylketeneimine ylide to afford a stable 1,3-dipolar addition product **60**, a pyrazole derivative (Eq. 3.27). Delocalization of the negative charge around the heterocyclic ring results in the high stability of the pyrazole derivative[1,76]:

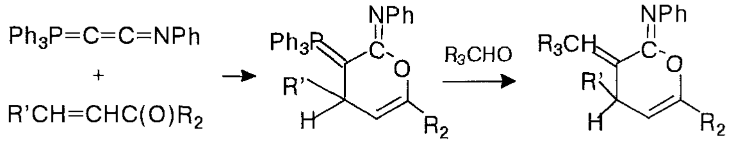


60

(3.27)

3.2.6 [4+2]-Cycloaddition Reactions

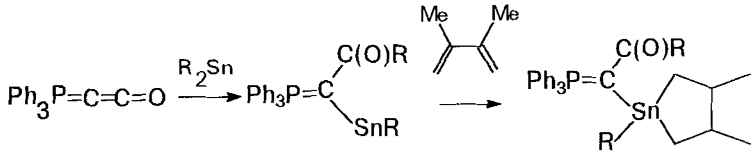
Bestmann reported that [4+2]-cycloaddition of triphenylphosphonium *N*-phenylketeneimine ylide with α,β-unsaturated ketones, vinylmethylketones, and some thioisocyanates leads to the formation of six-membered cyclic iminoether ylides, which undergo the Wittig reaction with aldehydes to afford arylmethylenes or alkylideneiminolactones (Eq. 3.28)[1,3]:



(3.28)

3.2.7 Miscellaneous Reactions

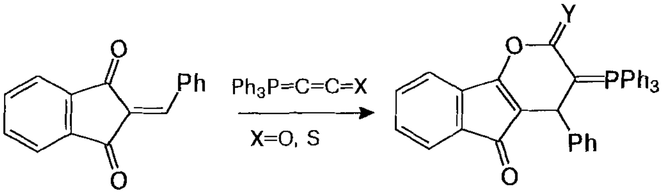
Ketene ylides add derivatives of two-coordinate tin to furnish C-tin-substituted ylides **61** in high yields. The latter readily enter into [1+4]-cycloaddition reactions with dienes to form C-tin-substituted ylides **62** (Eq. 3.29)[62]:



61 **62**

(3.29)

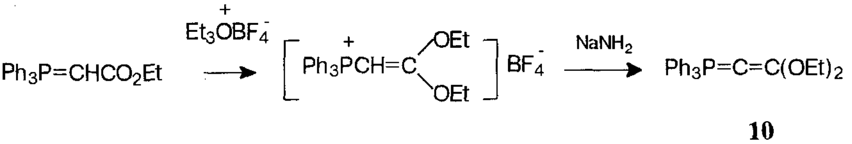
The reaction of electron-deficient exo-conjugated systems with phospha-cumulene ylides was described by Soliman and co-workers (Eq. 3.30)[63]:



(3.30)

3.3 Phosphaketeneacetal Ylides

Keteneacetal ylides can be obtained from triphenylphosphonium ethoxycarbonylmethylide. Alkylation of ethoxycarbonylmethylide with triethyloxonium tetrafluoroborate affords the vinylphosphonium salt, deprotonation of which with sodium amide results in the formation of phosphaketeneacetal ylide **10** (Eq. 3.31)[9,64–66]. The phosphadithioketene-acetal $Ph_3P{=}C{=}C(SR)_2$ was prepared analogously[67].

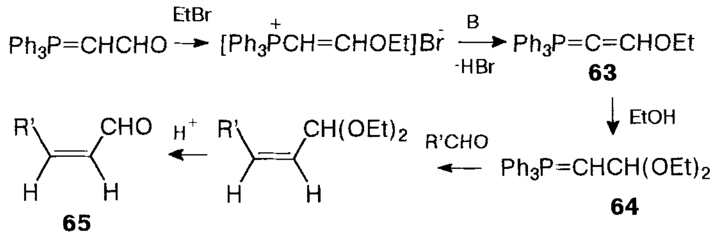


$$Ph_3P{=}CHCO_2Et \xrightarrow{Et_3\overset{+}{O}BF_4^-} \left[Ph_3\overset{+}{P}CH{=}C\begin{matrix}OEt\\OEt\end{matrix}\right]BF_4^- \xrightarrow{NaNH_2} Ph_3P{=}C{=}C(OEt)_2$$

10

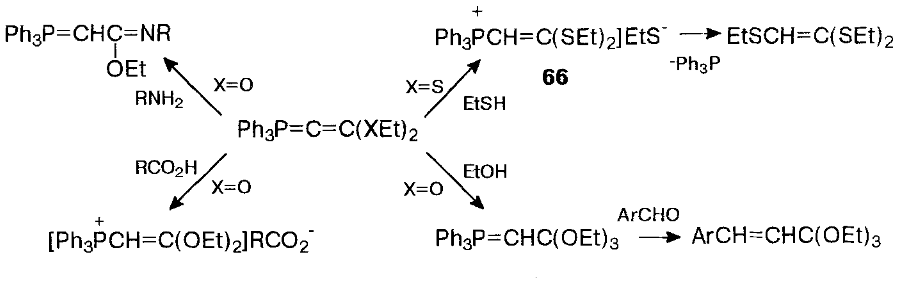
(3.31)

Alkylation of formylide with ethyl bromide and subsequent deprotonation of the vinylphosphonium salt by base affords the vinyl ylide, **63**, which has found application in organic synthesis (Scheme 3.18). Thus, the addition of ethanol to **63** leads to the formation of ylide **64** which undergoes the Wittig reaction with aldehydes and results in *Z*-α,β-unsaturated aldehyde acetals which can be converted into unsaturated aldehydes **65** by treatment with acid. Aldehydes have been used in the synthesis of *Z,Z*-diene fragments of various naturally occurring compounds.[24,41,66–68].



Scheme 3.18

Phosphonium ketenacetalylides add amines, carbonic acids, ethanol (Scheme 3.19)[69-72]. The reaction of keteneacetalylide with ethanol leads to the formation of highly reactive triphenylphosphonium 2,2,2-triethoxyethylide which readily undergoes the Wittig reaction with aldehydes.[69,72] At the same time reaction of dithioketeneacetalylide with ethanethiol, probably because of the instability of the intermediate addition product **66**, proceeds with elimination of triphenylphosphine to result in tris(ethanethiol) ethylene[71]:



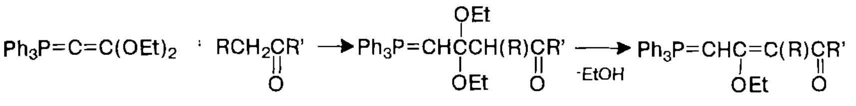
Scheme 3.19

Table 3.3. Phosphaketeneacetalylides $Ph_3P{=}C{=}C(R')XR$

XR	X	R'	mp	Yield, (%)	δ_P, ppm	Ref.
Et	O	H	65°C	69	11.69	66
Et	O	EtO	80-81	48		64
Me	S	MeS	55-60	65	-4.94	65,67
Et	S	Et S	63-67	71	-5.09	65,67
Pr	S	PrS	68-72	49	-4.96	65,67
Bu	S	Bu S	Oil	-	-5.05	65,67
Et	S	Me S	55-60	49	-4.94	65,67

Phosphaketeneacetals are strong bases and nucleophiles. The greater basicity of phosphaketeneacetals compared with phosphaketene ylides enables them to add such weak CH-acids as amines, acetophenone, ethyl acetate, and cyclohexanone[65,66].

Reaction proceeds via the formation of the Michael addition product, **67**, which eliminates ethanol to furnish the vinylphosphonium ylide (Eq. 3.32)[72,73].

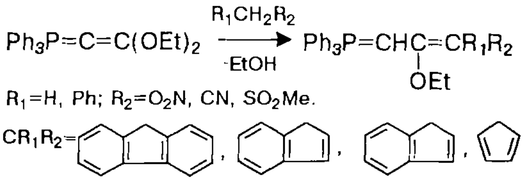


$$Ph_3P{=}C{=}C(OEt)_2 + RCH_2\underset{\overset{\|}{O}}{C}R' \longrightarrow Ph_3P{=}CH\underset{OEt}{\overset{OEt}{C}}CH(R)\underset{\overset{\|}{O}}{C}R' \xrightarrow[-EtOH]{} Ph_3P{=}CH\underset{OEt}{C}{=}C(R)\underset{\overset{\|}{O}}{C}R'$$

67

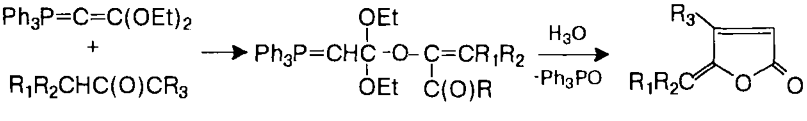
(3.32)

Phosphaketeneacetales afford Michael addition products with fluorene, indene, and acetonitrile also (Eq. 3.33)[19,67]:



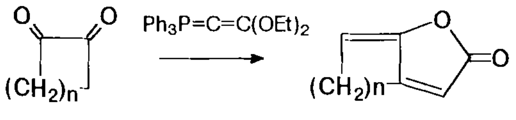
(3.33)

A new butenolide synthesis has been developed on the basis of the reaction of phosphaketeneacetal with enolized 1,2-diketones, which includes the acidic hydrolysis of the intermediate addition product (Eq. 3.34)[74]:



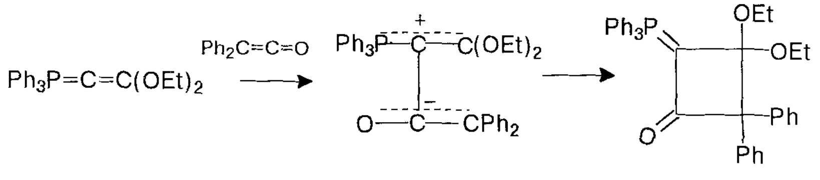
(3.34)

The reaction of cyclic 1,2-diketones with triphenylphosphonium keteneacetal ylide produces bicyclic 4-alkylidene-2-buten-4-ylides. Reaction proceeds via an enolate salt and the intramolecular Wittig reaction (Eq. 3.35)[74]:



(3.35)

Phosphaketeneacetal ylides undergo [2+2]-cycloaddition reactions with heterocumulenes. Thus keteneacetalylide reacts with diphenylketene to form a stable zwitterionic product which was detected by NMR. On heating to 30–40°C the zwitterion undergoes 1,4-cyclization to produce cyclobutanoneylide **68** (Eq. 3.36)[74]:

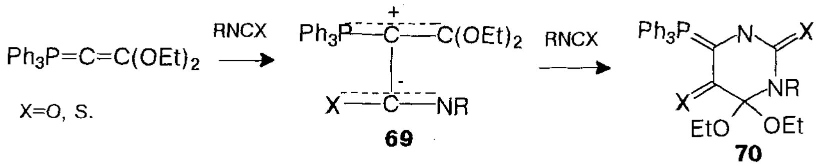


68

(3.36)

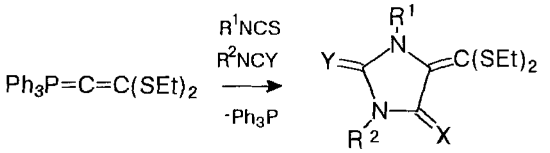
Reaction of phosphaketeneacetal with isocyanates and isothiocyanates affords dipolar products **69**, the positive charge of which is stabilized by ethoxy groups. These products undergo [4+2]-cycloaddition reactions with a second molecule of heterocumulene to produce six-membered cyclic product **70** bearing a phosphorus ylidic group (Eq. 3.37)[74].

The dithioketeneacetalylide reacts with isothiocyanates and isocyanates to form five-membered cyclic products **71** and triphenylphosphine (Eq. 3.38)[74]:



69 **70**

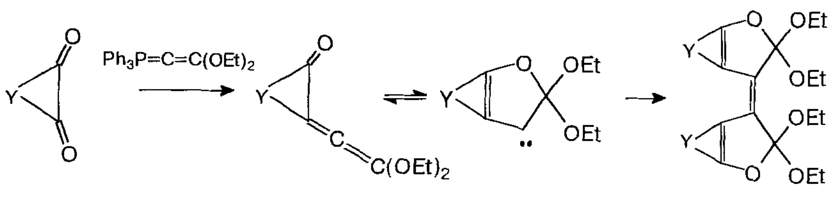
(3.37)



71

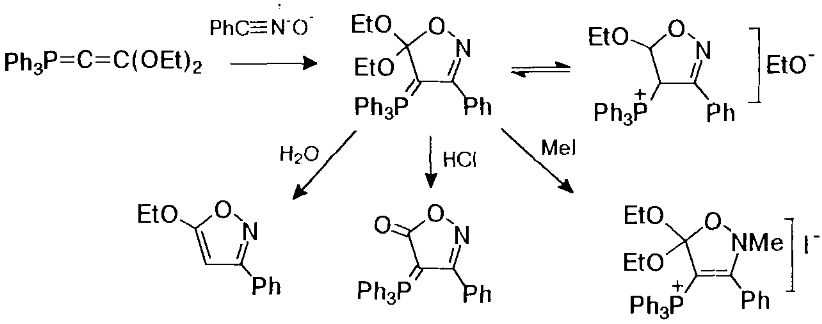
(3.38)

The reaction of triphenylphosphonium diethylacetalketeneylide with *o*-quinones results in olefins via the formation of carbenes (Eq. 3.39)[75]:



(3.39)

Triphenylphosphonium diethylacetalketenylide undergoes a cycloaddition reaction with phenyl nitrone to result in isoxazole derivatives, which exist in equilibrium with the phosphonium alcoholate. The isoxazole derivative is hydrolyzed to form the 5-ethoxy-3-phenylisoxazole, reacts with hydrochloric acid to afford the stable phosphorus ylide, and adds methyl iodide to furnish the phosphonium salt (Scheme 3.20)[3,76]:



Scheme 3.20

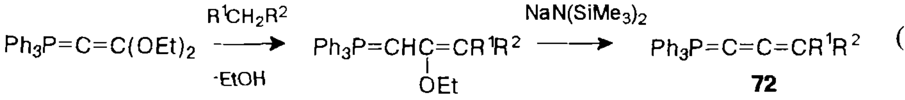
3.4 Phosphaallene Ylides and Phosphacumulene Ylides

The phosphaallene ylides were synthesized by reaction of the triphenylphosphonium methylide with geminal dihalogenides[16,77-80]. The reaction proceeds with a 3:1 ratio of initial reagents (Eq. 3.40). Phosphaallene ylides were isolated in good yields as crystalline compounds:

$$2Ph_3P{=}CH_2 \xrightarrow[-[Ph_3P^+Me]X^-]{X_2C{=}CR^1R^2} Ph_3P{=}CHC(X){=}CR^1R^2 \xrightarrow[-[Ph_3PMe]X]{Ph_3P{=}CH_2} Ph_3P{=}C{=}C{=}CR^1R^2 \quad (3.40)$$

$CR^1R^2{=}C(CO_2Me)_2$, $C(CN)CO_2Me$, CAr_2

The reaction of acetal ylides with CH-acids in the presence of $NaN(SiMe_3)_2$ gives rise to the formation of stable cumulene ylides 72 (Eq. 3.41, Table 3.4)[78]:



$$Ph_3P{=}C{=}C(OEt)_2 \xrightarrow[-EtOH]{R^1CH_2R^2} Ph_3P{=}CH\underset{\displaystyle OEt}{C}{=}CR^1R^2 \xrightarrow{NaN(SiMe_3)_2} \underset{\mathbf{72}}{Ph_3P{=}C{=}C{=}CR^1R^2} \quad (3.41)$$

Table 3.4. Phosphaallene Ylides **72** (Eq. 3.41)[19,78]

R^1	R^2	Yield, %	mp
Ph	CN	65	145-146°C
C_6H_4OMe-4	CN	47	128-130
Ph	CO_2Et	59	120-122
-CH=CHCH=CH-		51	163-165

Phosphaallene ylides have been prepared by dehydrohalogenation of vinylphosphonium salts with butyl lithium (Eq. 3.42)[79]:

$$Ph_3P + BrCH{=}CPh_2 \longrightarrow [Ph_3\overset{+}{P}CH{=}CPh_2]Br^- \xrightarrow{BuLi} Ph_3P{=}C{=}CPh_2 \xrightarrow{Ph_2C{=}O} Ph_2C{=}C{=}CPh_2 \qquad (3.42)$$

The dehydrochlorination of 2,3-dichloropropene-2-triphenylphosphonium salts by sodium bis(trimethylsilyl)amide leads to the formation of the triphenylphosphonium 3-chlorocumulene ylide, which undergoes the Wittig reaction to produce chlorocumulenes (Eq. 3.43)[77]:

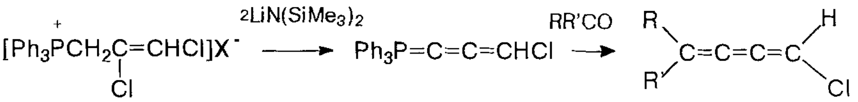

(43)

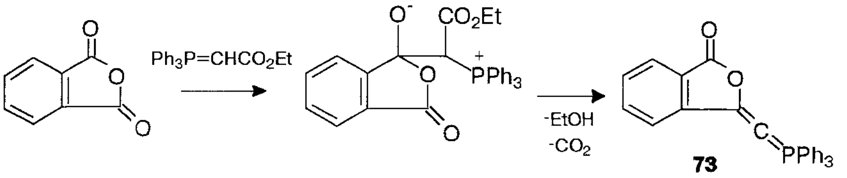
Table 3.5. Phosphacumulene ylides $Ph_3P{=}(C{=})_nCRR'$

R	R'	n	mp	Ref
H	H	2	-	101
Ph	CN	2	145-146°C	78,19
Ph	CO_2Me	2	120-122	78
C_6H_4OMe-4	CN	2	128-130	78
-CH=CHCH=CH-		2	163-165	78
CRR'=9-Fluorenylidene		2	188-189	17
CF_3	CF_3	1	-	16
Cl	H	1	-	77
Ph	Ph	1	-	81
Ph	Ph	2	-	79
Et	Et	2	-	81
i-Pr	i-Pr	2	-	81
Ph	Ph	2	-	81

Cumulene ylide **72** was prepared by treatment of the phosphonium salt with excess pyridine or triethylamine. The cumulene ylide, without isolation from the reaction mixture, was treated with diphenylketene to furnish tetraphenylcumulene in good yield (Eq. 3.44).[79]

$$Ph_3P + BrCH_2CH{=}CRR' \longrightarrow Ph_3\overset{+}{P}CH{=}C{=}CRR' \xrightarrow{Et_3N} \underset{\textbf{72}}{Ph_3P{=}C{=}C{=}CRR'} \qquad (44)$$

By heating triphenylphosphonium carboethoxymethylide with hexahydro-1,3-phthalanedione in toluene Boulos and Shabana[80] synthesized phosphaallene ylide **73** isolated as a crystalline substance in 41% yield (Eq. 3.45):



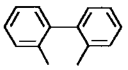
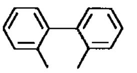
(3.45)

Phosphaallene ylides and phosphacumulene ylides (Eq. 3.46, Table 3.5) are convenient reagents for the synthesis of allenes and cumulenes (Eq. 3.46, Table 3.6)[16,75,77–82]:

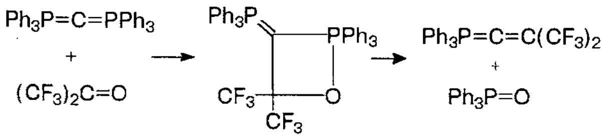
$$Ph_3P{=}C{=}CR^1R^2{+}R_3R_4C{=}O \longrightarrow R^1R^2C{=}C{=}CR^3R^4 \tag{46}$$

$$Ph_3P{=}C{=}C{=}CR^1R^2{+}R^3R^4C{=}O \longrightarrow R^1R^2C{=}C{=}C{=}CR^3R^4 \tag{47}$$

Table 3.6. Cumulenes (Eq. 3.47)

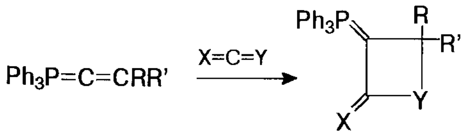
R^1	R^2	R^3	R^4	Yield (%)	Refs
Ph	Ph	4-$O_2NC_6H_4$	H	69	8
Ph	Ph	3,4-ClC_6H_3	H	80	8
H	H	C_6H_{11}	H	■	101
				71	16

The reaction of phosphaallenes with carbonyl compounds sometimes furnishes four-membered cyclic products. Thus a stable cyclo-adduct of triphenyl-phosphonium diphenylallene ylide and hexafluoroacetone was described by Birum and Matthews. On heating the cyclo-adduct was converted into triphenylphosphonium bis (trifluoromethyl)allene ylide and triphenylphosphine oxide (Eq. 3.48)[6]:



(3.48)

Stable four membered cyclic adducts of phosphaallene ylides with isocyanates and keteneimines have been synthesized (Eq. 3.49)[16]:



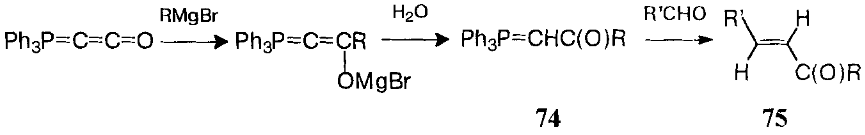
(3.49)

Phosphaallene ylides have been used for the synthesis of allenes and polyenes bearing the di-coordinated phosphorus atom (Eq. 3.50)[81]:

$$Ph_3P{=}C{=}CPh_2 + ArPHCl \longrightarrow ArP{=}C{=}CPh_2 \qquad (3.50)$$

3.5 Application in Natural Product Synthesis

Cumulene ylides have been widely used for the synthesis of natural products and several approaches to the synthesis of the structural fragments of pheromones, antibiotics, and biologically active compounds has been developed[2]. One such approach is the reaction of triphenylphosphonium ketene ylide with Grignard reagents resulting in a primarily addition product, subsequent hydrolysis of which yields acyl ylides **74** (Table 3.7) which undergo the Wittig reaction to furnish *E*-α,β-unsaturated ketones **75** (Eq. 3.51)[83-85]:

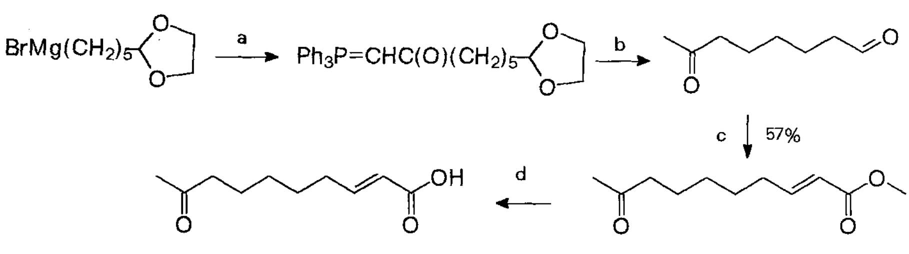


(3.51)

Table 3.7. Yields of ylides **74** and *E*-α,β-unsaturated ketones **75** (Eq. 3.51)

R	Yield of **74** (%)	R'	Yield of **75** (%)
Et	94	Me	54
Bu	85	Ph	52
s-Pnt	77	Ph	42
Ph	65	*E*-$CH{=}CH(CH_2)_2Me$	48
$CMe{=}CH_2$	86	C_7H_{15}	36

Bestmann and co-workers. used this reaction for the pheromone synthesis. Thus, the queen substance found in the secretions of honey bees, was synthesized by reaction of ketene ylide with alkylmagnesium halide as a key step. (Scheme 3.21)[85]:

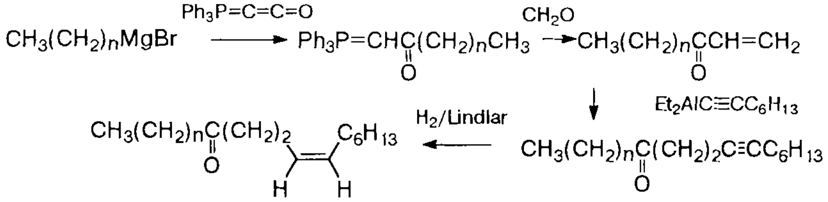


a = $Ph_3P{=}C{=}O$; b = $NaHCO_3$/THF, c = $Ph_3P{=}CHCO_2Me$; d = Na_2CO_3/H_2O, dioxane,Δ,5h

Scheme 3.21

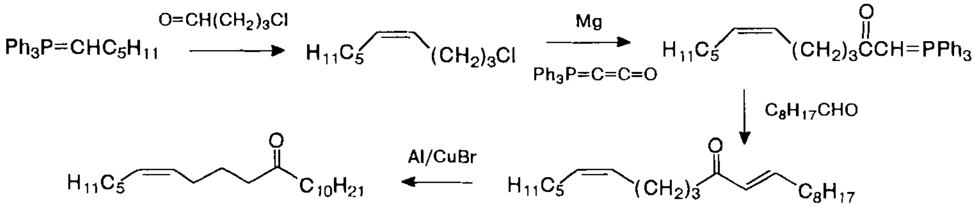
The Grignard reagent reacted with ketene ylide to afford an acyl ylide, hydrolysis of which led to the ketoaldehyde. .The latter reacted with the triphenylphosphonium carbomethoxymethylide to give rise to the olefin, which was hydrolyzed to the queen substance

The active compound of the sex pheromones of the peach fruit moth *Carposina niponensis* have been synthesized in four steps, using the chain-lengthening function of Grignard reagents by reaction with ketene ylide as the key step (Scheme 3.22)[85]:



Scheme 3.22

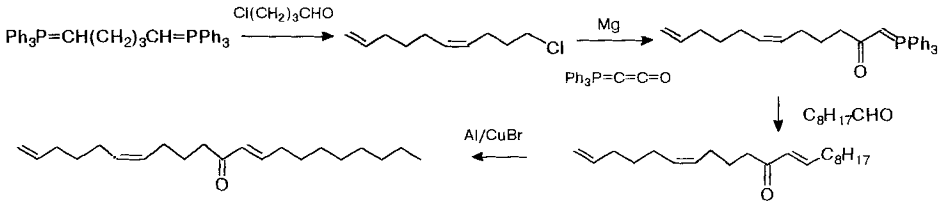
Principal and minor sex pheromone components of the Douglas-fir tussock moth *(Orgyia pseudotsugata)* have also been synthesized:



Scheme 3.23

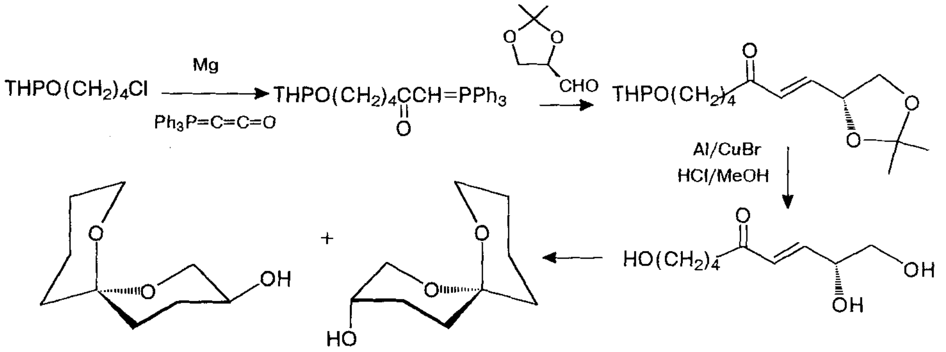
The key step in the both syntheses is the Grignard reaction with the triphenylphosphonium ketene ylide. The starting chloroolefin was prepared by reaction of triphenylphosphonium hexylide with ω-chlorobutyraldehyde and was then transformed into the corresponding organomagnesium derivative. The latter reacted with ketene ylide to give the acyl ylide. Subsequent reaction with nonanal furnished dienon, which was reduced to yield the primary pheromone component (Scheme 3.23).[85]

The second component of the pheromones of the Douglas-fir tussock moth was prepared by the cross-Wittig reaction of a bis-ylide with ω-chlorobutyraldehyde and formaldehyde in the 1:0.75:1.25 ratio. The reaction provided the diene chloride in 45% yield and the Grignard derivative of the diene chloride was reacted with the ketene ylide to give the acyl-ylide. Subsequent reaction of the acyl ylide with nonanal furnished the trienone which was partially reduced to result in the second pheromone component (Scheme 3.24):



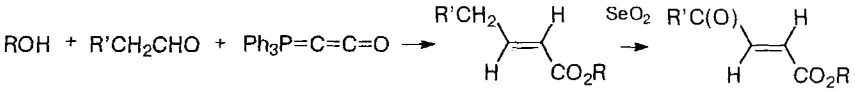
Scheme 3.24

The synthesis and separation of a diastereomeric mixture of 3*S*,6*R*- and 3*S*,6*S*-3-hydroxy-1,7-dioxaspiro-[5,5]-undecane, a component of the pheromone complex of the olive fly, *Dacus oliae*, was reported by Bestmann and Schmidt (Scheme 3.25)[86]. The first step of the synthesis is reaction of triphenylphosphonium ketene ylide with the Grignard derivative of 4-chlorobutanol ether, furnishing an acyl ylide. The latter reacted with the acetonide of glycerin aldehyde to afford an unsaturated ketone. Subsequent deprotection of this compound, via the formation of intermediate nonane-5-on-1,2,9-triol led to the formation of the *Dacus oliae* pheromone, as a optically pure pair of diastereomers which were separated by preparative chromatography.



Scheme 3.25

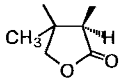
The preparatively convenient three-component reaction of triphenylphosphonium ketene ylide with alcohol and aldehyde selectively leads to the formation of a β-unsaturated ester. The reaction of ketene ylide with alcohol furnishes an ester ylide, which immediately reacts with aldehyde to produce the olefin **76** in high yields. Oxidation of the β-unsaturated ester **76** with SeO_2, affords a β-acylacrilic ester 77, the structural fragment of many macrocyclic natural products, in particular antibiotics. Bestmann and Schobert used this chemoselective tricomponent reaction to build up cyclic biologically active molecules (Eq. 3.52, Table 3.8)[87].



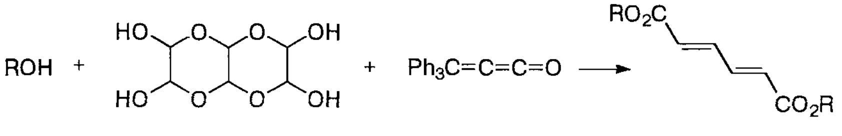
(3.52)

76 **77**

Table 3.8. α,β-Unsaturated esters **77** (Eq. 3.52)

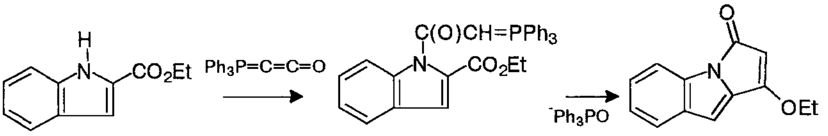
R	R'	Yield,(%)
C_6H_{13}	Bu	94
C_4H_9	Bu	92
s-Me(Et)CHCH$_2$	Pr	81
(-)-Ment	Pr	81
	Pr	55

The reaction of alcohols with triphenylphosphonium ketene ylide and glyoxal hydrate in 6:1:6 ratio provides the *E,E*-muconic acid ester (Eq. 3.53)[87,88].



(3.53)

A three-component chemoselective system has also been used for the preparation of cyclic compounds. For instance, 2-indole carboxylate reacts with triphenylphosphonium ketene ylide with the formation of an intermediate **78** which enters into the intramolecular Wittig reaction to result in a three-ring heterocyclic compound **79**, a structural fragment of mitomicin (Eq. 3.54)[38]:

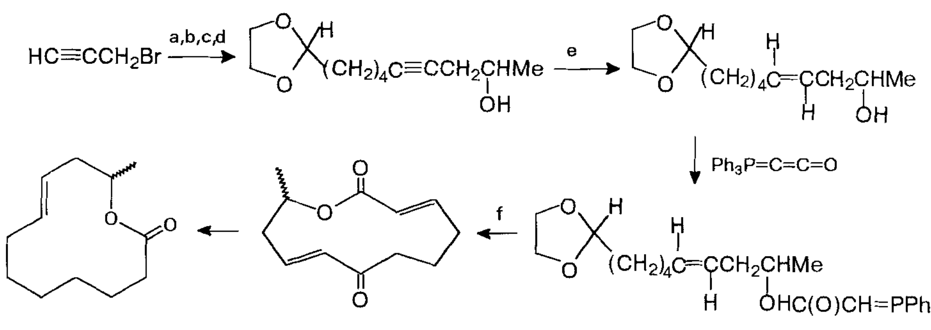


78 **79**

(3.54)

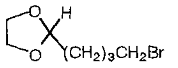
This reaction was used for the preparation of such macrocyclic lactones as *recifeiolid*, isolable from the bacterium *Cephalosporium recifei*. The unsaturated alcohol was prepared starting from propargyl bromide, and then converted into the *trans*-olefinic alcohol. The latter was converted into the acyl ylide **80** by reaction with ketene ylide. Subsequent acidic cleavage of the protecting groups liberated the lateral aldehyde group; this initiated the intramolecular Wittig reaction to give rise to the twelve-membered macrocyclic lactone **81**. Selective reduction of the *α,β*-double C=C bond provided the naturally occurring product *recifeiolid* **82** (Scheme 3.26)[90]:

The macrocyclic antibiotic A26771B was synthesized analogously (Scheme 3.27)[88]. Addition of an hydroxyaldehyde to ketene ylide furnished the intermediate acyl ylide which readily underwent intramolecular Wittig reaction to afford the macrocycle **83**. Oxidation of this compound with selenium dioxide led to the formation of the cyclic ketone **84**. Finally, reaction of the ketone with succinic anhydride provided the racemic macrocyclic antibiotic (±)-A26771B **85**



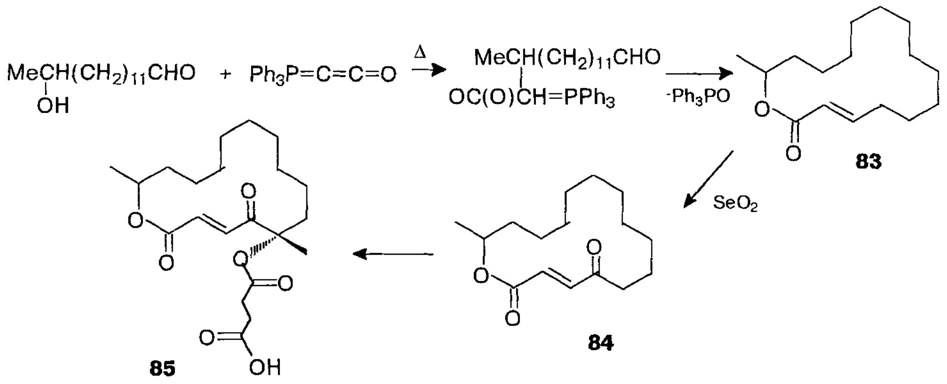
82 **81** **80**

a= Al/HgCl; b= MeCHO; c= LiNH2; d=



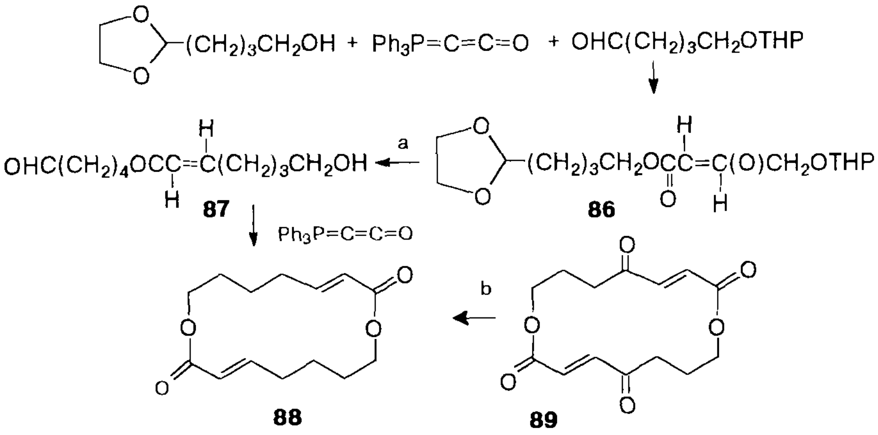
e= NaNH2/NH3; f= H⁺/H2O

Scheme 3.26



Scheme 3.27

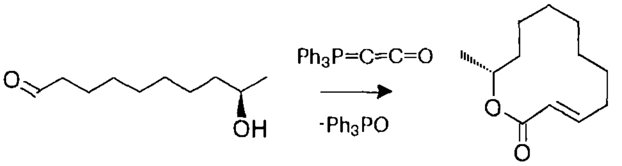
The next example of the synthesis of a naturally occurring macrocycle by means of chemoselective three-component systems is the preparation of norpyrenophorene. The starting compound was 5-hydroxypentane-1-ol (Scheme 3.28)[88]. Half of this reactant was protected at the aldehyde function and the other half at the hydroxy group as the THP derivative. These two parts of 5-hydroxypentanal were reacted with ketene ylide in three-component reaction to provide an olefin **86** containing protected aldehyde and hydroxyl groups. The protecting groups were then cleaved in acid medium. The resulting aldehydoalcohol **87** reacted with ketene ylide to form acyl ylide readily undergoing an intramolecular Wittig reaction to produce the cyclic product **88**. This product was oxidized with SeO_2 to provide *norpyrenophorene* **89** (Scheme 3.28)[88]:



a = H^+/H_2O; b= SeO_2

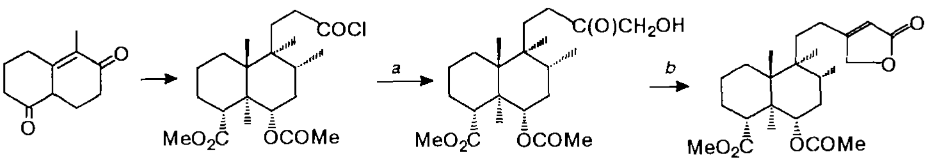
Scheme 3.28

Optically active *R*-(+)-patulolid A, isolated from *Penicillium urticae S11R59*, was obtained starting from 1,7-heptanediol and using the cyclization reaction of the ω-hydroxyaldehyde with ketene ylide (Eq. 3.55)[89]:



(55)

Triphenylphosphonium ketene ylide was also used in the synthesis of natural ajugarine-IV **90**, with insecticidal and antifeedant properties, starting from octalindione (Scheme 3.29): [91]



a - $Me_3SiOCH=C(SiMe_3)_2$; b - $Ph_3P=C=C=O$

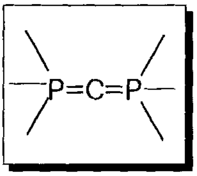
90

Scheme 3.29

In this instance the appropriate chloride was treated with tris(trimethylsiloxy) ethylene to afford an hydroxyketone which was transformed into (+)-ajugarine by reaction with triphenylphosphonium ketene ylide:

3.6 Carbodiphosphoranes

Carbodiphosphoranes are an interesting type of phosphorus ylide containing two cumulated ylide functions



Carbodiphosphoranes were prepared and isolated for the first time by Ramirez and co-workers in 1961[94] by deprotonation of ylide phosphonium salts with potassium. Heating of bis(triphenylphosphonium)methylylide bromide with potassium in dimethoxyethane furnishes hexaphenylcarbodiphosphorane in good yield (Eq. 3.56)[94–96]:

$$[Ph_3P{=}CH\overset{+}{P}Ph_3]Br^- \xrightarrow[-\,KBr,\ -H_2]{K} Ph_3P{=}C{=}PPh_3 \qquad (3.56)$$

Hexaphenylcarbodiphosphorane[94]

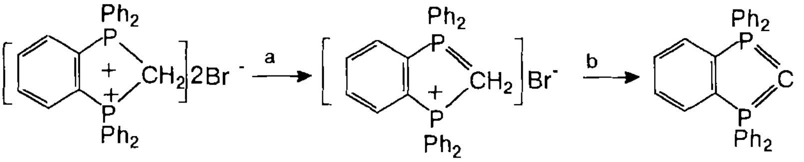
A suspension of potassium (~0.013–0.014 mol) in Vaseline oil was placed in a flask and washed with hexane. The hexane was removed under vacuum and bis(dimethoxy)ethane (150 mL) was added. The bis(triphenylphosphonium)methylide bromide was the added with vigorous stirring under nitrogen. The reaction mixture was stirred for 45 min at 120°C and the hot solution separated from potassium bromide by filtration. The yellow solution was evaporated under vacuum to approximately 70–80 mL and was left at room temperature overnight to provide the hexaphenylcarbodiphosphorane in 70% yield, mp 216–218°C

Carbodiphosphoranes **93** can be prepared by deprotonation of ylide phosphonium salts **91** formed by dehydrohalogenation of starting bis-phosphonium salts **92** by use of weak bases (Eq. 3.57). The reaction of salts **92** with sodium amide or butyllithium leads to abstraction of the second proton from the α carbon atom and the formation of carbodiphosphorane **93**[94–99]:

$$\underset{R=Alk,\ Ph}{R_3P} \xrightarrow{CH_2Br_2} \underset{\mathbf{91}}{[R_3\overset{+}{P}CH_2\overset{+}{P}R_3]2Br^-} \longrightarrow \underset{\mathbf{92}}{[R_3P{=}CH\overset{+}{P}R_3]Br^-} \xrightarrow{B} \underset{\mathbf{93}}{R_3P{=}C{=}PR_3} \qquad (3.57)$$

Thus, treatment of cyclic bis-phosphonium salts with ammonia or butyllithium affords ylide phosphonium salts which can be deprotonated by triethylphosphonium ethylide.

The resulting cyclic carbodiphosphorane **94** was isolated as a yellow crystalline solid stable at –40°C (Eq. 3.58)[98]:

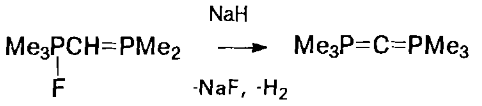


a = NH3, b = Et3P=CHMe

94

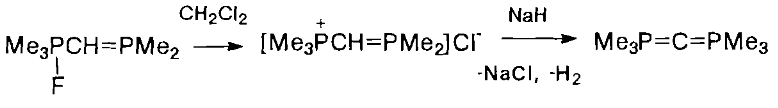
(3.58)

Heating the trimethylphosphonium trimethylfluorophosphoranemethylide with sodium hydride leads to the formation of the hexamethylcarbodiphosphorane in very good yield; this was isolated as a colorless distillable liquid. Deprotonation of the ylide phosphorane can be also realized by the action of butyllithium (Eq. 3.59)[97,99,100]:



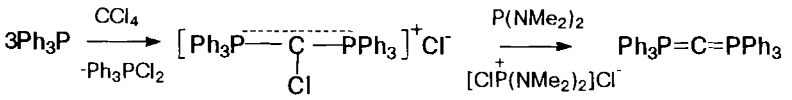
$$\underset{\textstyle F}{Me_3PCH{=}PMe_2} \xrightarrow[-NaF,\ -H_2]{NaH} Me_3P{=}C{=}PMe_3 \qquad (3.59)$$

Exchange of the fluorine atom in the ylide phosphorane for a chlorine atom and subsequent heating of ylide phosphonium salt with sodium hydride also gives rise to the hexamethylcarbodiphosphorane in very good yield (Eq. 3.60)[100]:



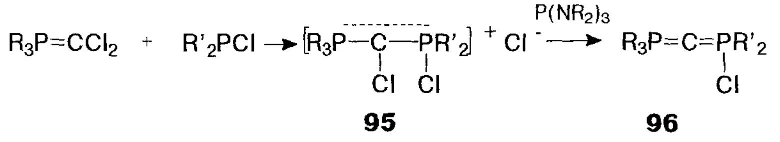
$$\underset{\textstyle F}{Me_3PCH{=}PMe_2} \xrightarrow{CH_2Cl_2} [Me_3\overset{+}{P}CH{=}PMe_2]Cl^- \xrightarrow[-NaCl,\ -H_2]{NaH} Me_3P{=}C{=}PMe_3 \qquad (3.60)$$

Ylide phosphonium salts formed by treatment of triphenylphosphine with carbon tetrachloride are readily dehydrochlorinated by tris(dimethylamino) phosphine to furnish carbodiphosphoranes in good yields (Eq. 3.61)[96,123]:



$$3Ph_3P \xrightarrow[-Ph_3PCl_2]{CCl_4} [Ph_3P{-}\underset{\textstyle Cl}{C}{-}PPh_3]^+Cl^- \xrightarrow[{[Cl\overset{+}{P}(NMe_2)_2]Cl^-}]{P(NMe_2)_2} Ph_3P{=}C{=}PPh_3 \qquad (3.61)$$

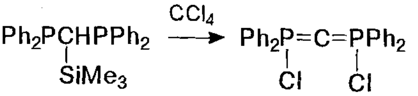
Phosphoric acid triamides have been used to convert haloalkylphosphonium salts into P-halogenated carbodiphosphoranes (Eq. 3.62). The dechlorination of the phosphonium salts **95** with tris(dimethylamino)phosphine in dichloromethane at room temperature gives carbodiphosphoranes **96** in high yield[102]:



$$R_3P{=}CCl_2 + R'_2PCl \rightarrow \underset{\mathbf{95}}{[R_3P\text{—}\underset{Cl}{C}\text{—}\underset{Cl}{P}R'_2]^+ Cl^-} \xrightarrow{P(NR_2)_3} \underset{\mathbf{96}}{R_3P{=}C{=}\underset{Cl}{P}R'_2} \qquad (3.62)$$

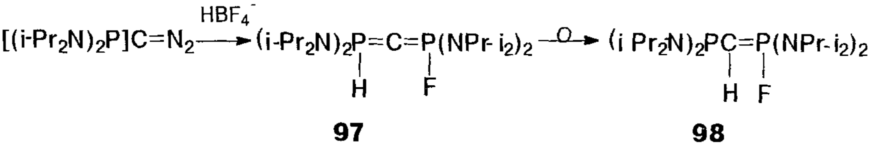
R=Ph, Me2N, Et2N, R=Me2N, Et2N

In recent years several carbodiphosphoranes of unusual structure with fluorine, chlorine, or even hydrogen atoms on the phosphorus atoms have been described[102–112]. Thus reaction with tetrachloromethane of tervalent phosphorus compounds containing a trimethylsilyl group on the *a* carbon led to the *P*-chlorocarbodiphosphorane (Eq. 3.63)[102,113]:



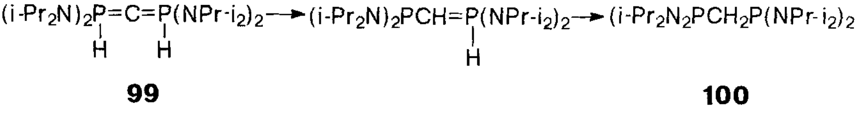
$$Ph_2P\underset{SiMe_3}{C}HPPh_2 \xrightarrow{CCl_4} Ph_2\underset{Cl}{P}{=}C{=}\underset{Cl}{P}Ph_2 \qquad (3.63)$$

Bertrand and Baceiredo found that carbodiphosphorane **98** with a P–H bond can be obtained directly by addition of tetrafluoroboric acid to diphosphine diazomethane. Carbodiphosphorane **97** is thermally quite stable as a solid (mp 116°C). In solution it slowly rearranges into the isomeric phosphorus ylide **98** (Eq. 3.64)[105]:



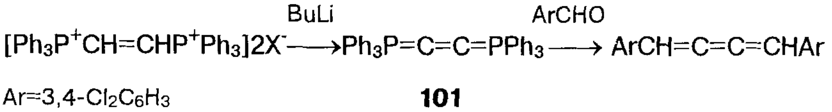
$$[(i\text{-}Pr_2N)_2P]C{=}N_2 \xrightarrow{HBF_4^-} \underset{\mathbf{97}}{(i\text{-}Pr_2N)_2\underset{H}{P}{=}C{=}\underset{F}{P}(NPr\text{-}i_2)_2} \xrightarrow{\Omega} \underset{\mathbf{98}}{(i\text{-}Pr_2N)_2P\underset{H}{C}{=}\underset{F}{P}(NPr\text{-}i_2)_2} \qquad (3.64)$$

Carbodiphosphorane **99** with a P–H bond is, however, unstable and is converted into the aminophosphine **100** as a result of a prototropic shift (Eq. 3.65)[106]:



$$\underset{\mathbf{99}}{(i\text{-}Pr_2N)_2\underset{H}{P}{=}C{=}\underset{H}{P}(NPr\text{-}i_2)_2} \rightarrow (i\text{-}Pr_2N)_2PCH{=}\underset{H}{P}(NPr\text{-}i_2)_2 \rightarrow \underset{\mathbf{100}}{(i\text{-}Pr_2N_2PCH_2P(NPr\text{-}i_2)_2} \qquad (3.65)$$

The unstable cumulene bis-ylide **101** was generated by treatment of a phosphonium salt with butyllithium and trapped with 3,4-dichlorobenzaldehyde (Eq. 3.66)[114]:

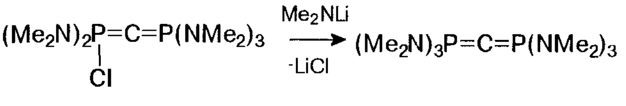


$$[Ph_3P^+CH{=}CHP^+Ph_3]2X^- \xrightarrow{BuLi} \underset{\mathbf{101}}{Ph_3P{=}C{=}C{=}PPh_3} \xrightarrow{ArCHO} ArCH{=}C{=}C{=}CHAr \qquad (3.66)$$

Ar=3,4-Cl2C6H3

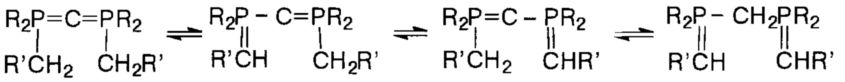
Symmetrically substituted carbodiphosphoranes have been obtained in high yield by reaction of *P*-chlorocarbodiphosphorane with organolithium compounds(Eq. 3.67.

Table 3.9)[115,116]. The fluorine atoms of *P*-fluorocarbodiphosphoranes are readily replaced by alkyl groups on reaction with organolithium compounds [117].



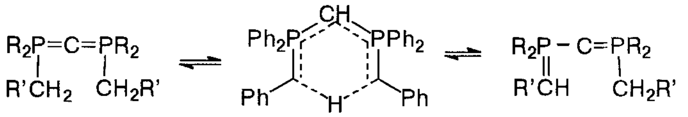
$$(Me_2N)_2\underset{Cl}{P}=C=P(NMe_2)_3 \xrightarrow[-LiCl]{Me_2NLi} (Me_2N)_3P=C=P(NMe_2)_3 \qquad (3.67)$$

Carbodiphosphoranes are of average thermal stability, and are strongly basic and highly reactive compounds. They react with variety of electrophiles. NMR spectra show that carbodiphosphoranes with alkyl groups on the phosphorus atom exist as an equilibrium mixture of prototropic tautomers (Eq. 3.68)[100,118,119]. The position of the tautomeric equilibrium depends on the electronic effect of the substituents. Electron-withdrawing substituents shift the equilibrium towards the bis-ylide form.



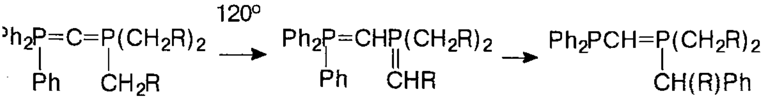
$$\underset{R'CH_2}{R_2P}=C=\underset{CH_2R'}{PR_2} \rightleftharpoons \underset{R'CH}{\overset{}{R_2P}}-C=\underset{CH_2R'}{PR_2} \rightleftharpoons \underset{R'CH_2}{R_2P}=C-\underset{CHR'}{PR_2} \rightleftharpoons \underset{R'CH}{R_2P}-CH_2\underset{CHR'}{PR_2} \qquad (3.68)$$

Prototropic exchange between the tautomers is probably intramolecular, proceeding through a six-membered transition state (Eq. 3.69)[119]:



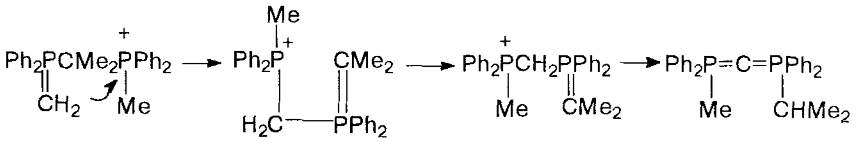
(3.69)

Some carbodiphosphoranes undergo rearrangement accompanied by migration of alkyl or phenyl groups. Thus, on heating to 120°C, asymmetric trialkylsubstituted carbodiphosphoranes give ylides via the formation of a bis-ylides as a result of migration of a phenyl group from the phosphorus atom to the ylide carbon atom (Eq. 3. 70)[96,122]:



$$h_2\underset{Ph}{P}=C=\underset{CH_2R}{P}(CH_2R)_2 \xrightarrow{120^{o}} Ph_2\underset{Ph}{P}=CH\underset{CHR}{P}(CH_2R)_2 \longrightarrow Ph_2PCH=\underset{CH(R)Ph}{P}(CH_2R)_2 \qquad (3.70)$$

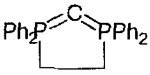
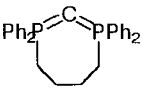
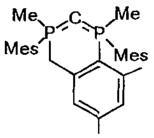
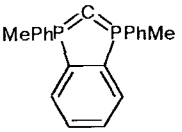
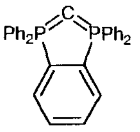
Ylide phosphonium salts **102**, with a dimethylmethylene group between the two phosphorus atoms, are unstable and rearrange through a four-membered transition state into carbdiphosphoranes, **103**. As a result of the rearrangement less sterically hindered compounds, **103**, are formed (Eq. 3.71)[124]:



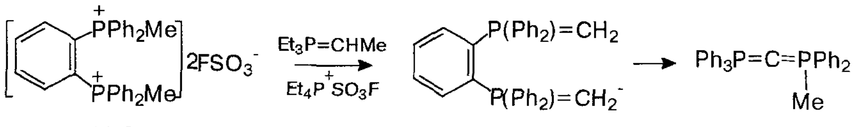
102 **103**

(3.71)

Table 3.9. Carbodiphosphoranes

Compound	Ref	Compound	Ref
$Me_3P=C=PMe_3$	97,99,100,140,146	$MePh_2P=C=PPh_2CH_2Mes$	118
$Me_3P=C=PPh_3$	125	$MesCH_2Ph_2P=C=PPh_2CH_2Mes$	118
$Et_3P=C=PPh_3$	96	$FcCH_2Ph_2P=C=PPh_2CH_2Fc$	160
$Pr_3P=C=PPh_3$	96	$[MePh_2P=C=PPh_2CH_2CH_2CH_2]_2$	121
$Bu_3P=C=PPh_3$	96	$(Me_2N)_3P=C=P(NMe_2)_3$	103
$MePh_2P=C=PPh_3$	125	$(i\text{-}Pr_2N)_3P(H)=C=P(H)(NMe_2)_2$	106
$Me_2PhP=C=PPh_3$	125	$Ph_2P(Cl)=C=P(Cl)Ph_2$	102,113
$MePh_2P=C=PPh_2Me$	120,126,147,149	$Ph_2P(Cl)=C=PPh_3$	102
$Me_2PhP=C=PPhMe_2$	126	$(Et_2N)_2P(F)=C=P(F)(NEt_2)_3$	110
$MePh_2P=C=PPh_2Pr\text{-}i$	122,124	$Ph_3P=C=P(Cl)(NEt_2)_2$	102
$Ph_3P=C=PPh_3$	94,131,143,155, 157,158	$(Me_2N)_3P=C=PPh_3$	103
		$(Me_2N)_3P=C=P(Cl)(NMe_2)_2$	103,115,116
	159	$c\text{-}Pr(Ph_2)P=C=P(Ph_2)Me$	161
	120,149, 159		118b
	98		98

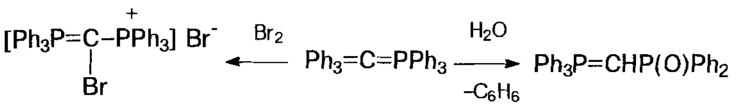
Transylidation of 1,2-bis-phosphonium benzene **104** with excess triethylphosphonium ethylide provides an unstable bis-ylide **105**, which readily rearranges into the carbodiphosphorane (Eq. 3.72)[125]:



104 **105**

(3.72)

The reaction of hexaphenylcarbodiphosphorane with bromine leads to the bromomethylide **106** (Eq. 3.73)[94]: Hydrolysis of hexaphenylcarbodiphosphorane proceeds with elimination of benzene and formation of the triphenylphosphonium oxodiphenylphosphinomethylide **107**[94,126]:

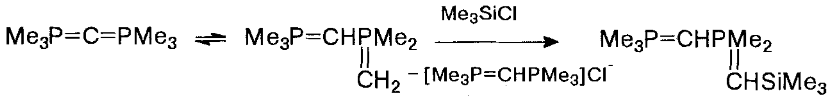


$$[Ph_3P{=}\underset{\displaystyle Br}{\overset{+}{C}}{-}PPh_3]\,Br^- \xleftarrow{Br_2} Ph_3{=}C{=}PPh_3 \xrightarrow[-C_6H_6]{H_2O} Ph_3P{=}CHP(O)Ph_2$$

106 **107**

(3.73)

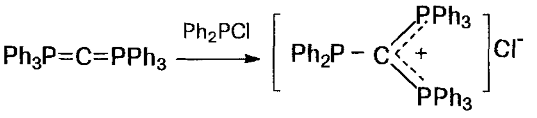
Carbodiphosphoranes are highly basic and nucleophilic. Reaction of carbodiphosphoranes with electrophiles gives products of replacement at the central or lateral carbon atoms. For instance, reaction of hexamethylcarbodiphosphorane with trimethylchlorosilane affords an ylide bearing the trimethylsilyl group on the lateral carbon atom (Eq. 3.74)[141].



$$Me_3P{=}C{=}PMe_3 \rightleftharpoons Me_3P{=}CH\underset{\displaystyle \overset{\|}{CH_2}}{P}Me_2 \xrightarrow[-[Me_3P=CHPMe_3]Cl^-]{Me_3SiCl} Me_3P{=}CH\underset{\displaystyle \overset{\|}{CHSiMe_3}}{P}Me_2$$

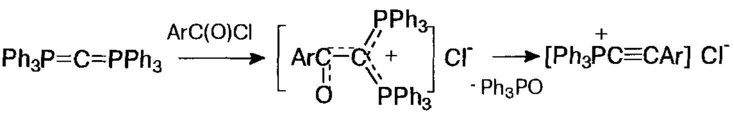
(3.74)

Alkylation of carbodiphosphoranes usually proceeds at the ylidic carbon atom to result in ylide phosphonium salts. In contrast, reaction of carbodiphosphoranes with alkyl halides, chlorophosphines, and acid chlorides usually occurs at the ylide carbon atom with the formation of the corresponding ylide phosphonium salts. Hexaphenylcarbodiphosphorane adds diphenylchlorophosphine to the ylide carbon atom to form the phosphonium salt (Eq. 3.75). X-ray crystallographic and NMR spectral analysis show that the compound's triphenylphosphonium groups are non-equivalent because of the hindered rotation of the diphenylphosphine group[127]:



(3.75)

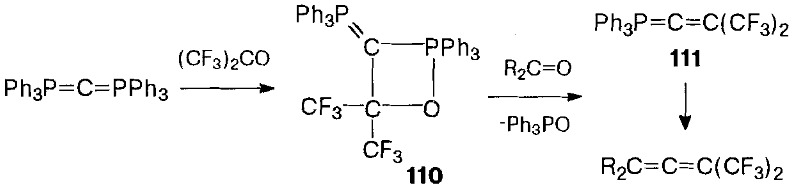
On the reaction with aromatic acid chlorides, hexaphenylcarbodiphorane gives C-acylated ylide phosphonium salts, **108**, which upon heating undergo an intramolecular Wittig reaction to provide arylethynylphosphonium salts, **109** (Eq. 3.76)[128].



108 **109**

(3.76)

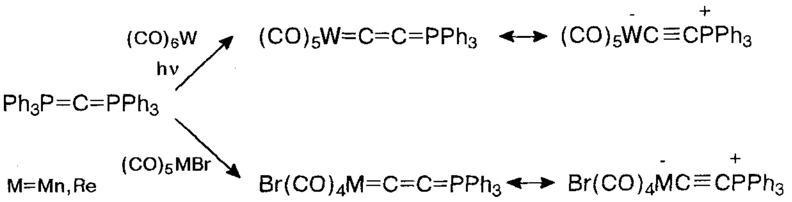
The carbodiphosphoranes are highly reactive compounds of high nucleophilicity and thus should react readily with aldehydes and ketones. Nevertheless reported examples of the reaction of carbodiphosphoranes with carbonyl compounds are very rare. Thus Birum and Matthews found in 1967 that the hexaphenylcarbodiphosphorane reacts with hexafluoroacetone to afford four-membered cyclic oxaphosphetanes, **110**, which are stable at room temperature and can be characterized by NMR. On heating, the oxaphosphetanes **110** are transformed into unstable alleneylides **111**, which undergo the Wittig reaction to produce tetra-substituted allenes (Scheme 3.30)[99]:



Scheme 3.30

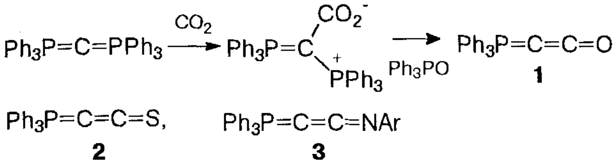
The reaction of the hexaphenylcarbodiphosphorane with metal carbonyls is accompanied by Wittig olefination to provide cumulene ylides (Scheme 3.31; M = W, Mn, Re).

X-ray crystallography showed that the negative charge of the conjugated bond system in the ylides is located on the metal and that the contribution of the resonance structure with the triple C≡C bond in the ground state is comparatively high.

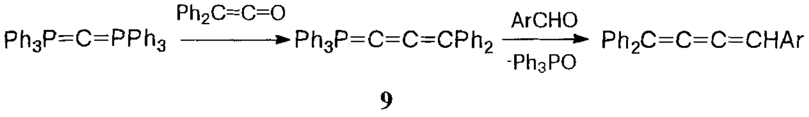


Scheme 3.31

With carbon dioxide, carbodiphosphoranes form betaines which can be isolated, characterized, and after heating, transformed into triphenylphosphonium ketenes **1** (Eq. 3.77). Triphenylphosphonium thioketenes **2** and triphenylphosphonium keteneimines **3** have been obtained analogously[129–132]. The reaction of carbodiphosphorane with diphenylketene yields a cumulene ylide which readily undergoes Wittig reactions with aldehydes to form cumulenes **9** (Eq. 3.78)[133]:



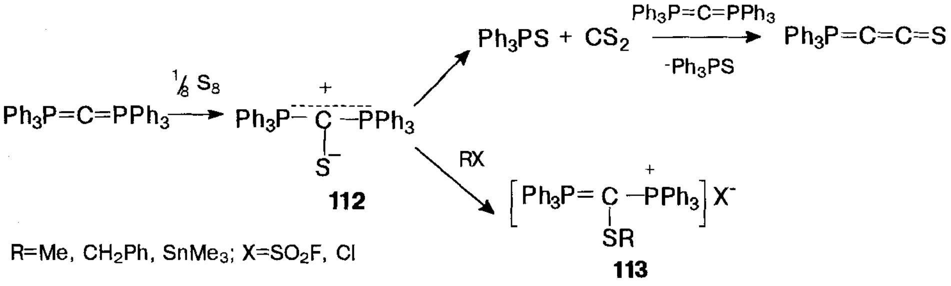
(3.77)



$$Ph_3P{=}C{=}PPh_3 \xrightarrow{Ph_2C{=}C{=}O} \underset{\mathbf{9}}{Ph_3P{=}C{=}C{=}CPh_2} \xrightarrow[-Ph_3PO]{ArCHO} Ph_2C{=}C{=}C{=}CHAr$$

(3.78)

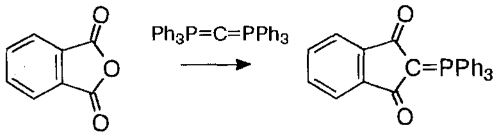
In THF at −50°C hexaphenylcarbodiphosphorane adds sulfur to form betaine **112** which is stable in solution at 0°C and which can be crystallized at −50°C as a red solid (Scheme 3.32).



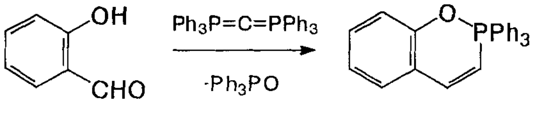
Scheme 3.32

Alkylation of betaine **112** proceeds with the formation of a phosphonium salt **113**. Addition of selenium to hexaphenylcarbodiphosphorane leads to the formation of a betaine stable at room temperature and identified by X-ray crystallography[134].

The reaction of hexaphenylcarbodiphosphorane with aromatic dicarboxylic acid and anhydrides such as phthalic acid anhydride proceeds with exchange of the anhydride oxygen atom for the ylide function to form cyclic ylides (Eq. 3.79)[128]. Hexaphenylcarbodiphosphorane reacts with the salicylaldehyde to give the six-membered cyclic oxaphosphorane (Eq. 3.80)[135]. The reaction probably proceeds via an intermediate.

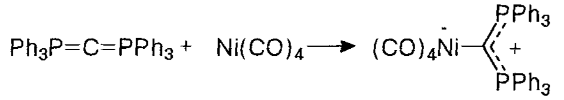


(3.79)

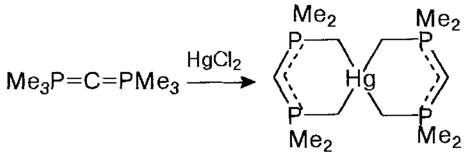


(3.80)

Carbodiphosphoranes are widely used as ligands for the preparation of transition metal complexes (Eq. 3.81,82)[137]. Ylide complexes containing carbodiphosphorane ligands have been reviewed in detail[137–139].


$$Ph_3P{=}C{=}PPh_3 + Ni(CO)_4 \longrightarrow (CO)_4\overset{-}{Ni}{-}\overset{+}{C}(PPh_3)_2$$

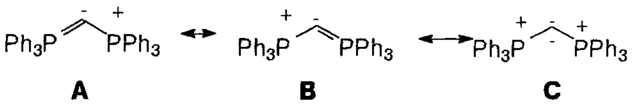
(3.81)



(3.82)

3.6.1 Structural Studies of Carbodiphosphoranes

The chemical and physicochemical properties of the compounds show that the diylide resonance formula **C** predominates in the ground state of carbodiphosphoranes (Eq. 3.83).



(3.83)

X-ray crystallography and electron diffraction data have proved that carbodiphosphoranes are dicarbanions. The central carbon atom of the carbodiphosphoranes has a hybridization close to sp^2, and the ground state of the carbodiphosphoranes can be described by the canonical structures **A**, **B**, and **C**[140–150] Thus, the molecular structure of hexamethylcarbodiphosphorane in the gas state was identified by electronography[146]. The length of the P=C bond is shortened to 1.594(3) Å whereas the length of the C–P bond is 1.814(3) Å. The P=C=P angle is 147.6(5)° greatly different from that of C=C=C in allenes which is close to 180°. The central carbon atom of carbodiphosphoranes has hybridization close to sp. Dipole moments of carbodiphosphoranes have also been determined: *m* (benzene) 4.69–0.05 D[151,152].

The structure of hexaphenylcarbodiphosphorane has been studied in detail because of its interesting triboluminescent properties (i.e. its capacity to generate light when stimulated mechanically)[154–158]. Hexaphenylcarbodiphos-phorane has polymorphic crystalline forms, in particular rhombic crystals without triboluminescent properties and microcrystalline triboluminescent monoclinic crystals. The main difference between these crystalline forms is related to the values of the P=C=P angles and C–P–P–C dihedral angles.

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Phosphorus Ylides: Chemistry and Application in Organic Synthesis
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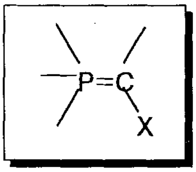
4 C-Heterosubstituted Phosphorus Ylides

4.1 Introduction

The chemistry of phosphorus ylides containing different heteroatom elements (metals and metalloids) on the α carbon atom has attracted considerable interest in recent years[1–14]. As a result of these studies phosphorus ylides containing elements from almost all groups of the periodic table have been synthesized and areas of their practical application in organic synthesis have been discovered. The chemical properties of C-heterosubstituted ylides are extremely diverse, because of the variety of the substituent elements and their different effects on the electron-density distribution in ylide molecules.



X = RO, R_2N, RS, Hlg, R_3Si, R_2P, Li, R_2B, RHg, R_3Zr, etc.

The stability of C-substituted ylides has made them fascinating and convenient objects for theoretical studies, particularly for study of the nature of the element–carbocation bond. Depending on the nature of the element this bond can be covalent or coordinate with various amounts of negative charge transfer from the carbanion to the element (Eq. 4.1):

$$R_3P{=}CH_2-E \longleftrightarrow R_3\overset{+}{P}-\overset{-}{C}H_2\leftarrow E \longleftrightarrow R_3\overset{+}{P}-CH_2=\overset{-}{E} \qquad (4.1)$$

Thus the elements of the higher periods which have vacant orbitals (silicon, phosphorus, sulfur, arsenic, etc.) interact with the ylide carbanion by a p_p-d_p-mechanism, resulting in a decrease in the electron density on the α carbon atom and partial element–carbon double bonding. On the other hand the elements with *s*-donating properties, e.g. mercury, increase the electron density on ylide carbon thus increasing further the already high nucleophilicity of the ylides. Also certain elements, especially transition metals, can form additional coordinate bonds with the ylide carbon atom. Sometimes the distribution of the electron density in the ylide molecule is simultaneously affected by two or even three different factors, their relative contribution depending on the nature of the element and the surrounding ligands.

C-substituted phosphorus ylides attract particular interest as reagents for organic synthesis, and thus find increasing application in laboratory practice and industry. For example, C-silicon phosphorus ylides have served as the basis for a series of preparative syntheses of medicinal, pheromone, and other types of phosphorus ylide. C-Phosphino phosphorus ylides are important ligands in transition-metal complexes. C-Halo phosphorus ylides are of interest for the preparation of haloalkenes. C-Nitrogen ylides are of considerable importance, especially in the synthesis of antibiotics.

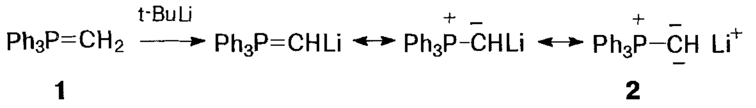
Numerous papers and patents on applications of C-substituted phosphorus ylides in various fields of organic synthesis have been generalized in several monographs[3,6,8] and reviews[1,2,10–13]. This present chapter summarizes data on the application in organic synthesis of phosphorus ylides substituted on the α carbon atom by atoms of elements of Groups I–VII

4.2 Phosphorus Ylides Substituted on the α-Carbon by Atoms of Element Groups I–IV

The influence of the σ-donor inductive and π-acceptor mesomeric effects of the elements is clearly exemplified by ylides containing metals and metalloids of the main subgroups of Groups I–IV of the periodic table on the a carbon atom. The elements with σ-donor properties increase the electron density on the ylide carbon atom, thus changing the nucleophilicity and reactivity of the ylides, as for instance, in the case of C-lithiated ylides. In contrast, such elements as germanium and silicon reduce the electron density on the α carbon atom thus forming partial element–carbon double bonding by a $p\pi$-$d\pi$ mechanism that results in lowering of the nucleophilicity of the ylide. Often these two opposite effects act together, and their relative contribution depends on the nature of element and the surrounding ligands. The chemistry of ylides containing lithium, boron, silicon, tin, and other elements on the a carbon atom has recently received considerable attention.

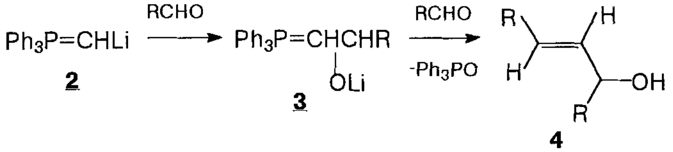
4.2.1 Ylides Containing Group IA and IIA Elements

The synthesis of ylides containing alkali metals on the ylide carbon atom presents a challenging problem. According to the definition of A. Johnson ylides are carbanions stabilized by the positively charged heteroatom[8]. The introduction of a Group I atom to the carbon considerably increases the electron density on this atom: the ylide carbanion thus becomes a dicarbanion. Quantum-chemical calculations performed by McDowell and Streitwieser[15] and by Bestmann[16] demonstrated that lithium methylides should have high nucleophilicity and reactivity. Because of the presence of a highly ionized C–Li bond they are associated in solution. The theoretical calculations were confirmed experimentally by Corey and Kang[17] who, pursuing the goal of preparation of 'hyperactive phosphorus ylides', synthesized lithium triphenylphosphonium methylide **2** by reaction of *tert*-butyllithium with triphenylphosphonium methylide **1** in THF at –78 to –40°C (Eq. 4.2).



$$\underset{\mathbf{1}}{Ph_3P{=}CH_2} \xrightarrow{t\text{-BuLi}} Ph_3P{=}CHLi \longleftrightarrow Ph_3\overset{+}{P}{-}\overset{-}{C}HLi \longleftrightarrow \underset{\mathbf{2}}{Ph_3\overset{+}{P}{-}\underset{-}{\overset{-}{C}}H\ Li^+} \qquad (4.2)$$

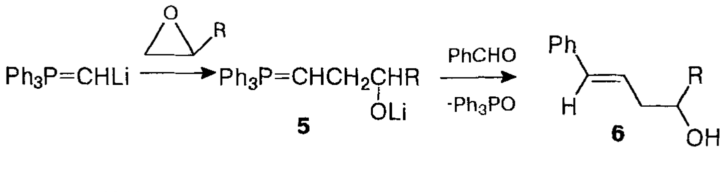
Ylide **2** manifests interesting chemical properties. It proved to be much more reactive than the initial triphenylphosphonium methylide. For example, the sterically hindered ketone, fenchone, does not react with triphenylphosphonium methylide on heating to 50°C, but can be easily alkenated by lithium methylide at –50°C to –20°C, in 1 h, to give the oxomethylene derivative (yield 87%)[17]. Lithium methylide **2** exchanges the metal atom for different groups in reactions with chlorine-containing electrophiles. It can also be introduced into a double Wittig reaction with aldehydes (SCOOPY-olefination) (Eq. 4.3).



(4.3)

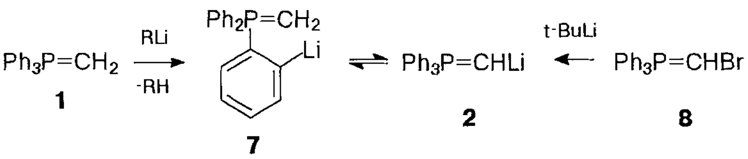
In reactions with aldehydes, lithium methylide **2** first forms alkoxide anions **3** which can enter into the Wittig reaction with a second molecule of a carbonyl compound to form *trans*-allylic alcohols **4**[17].

Reaction of α–lithiated ylide **2** with epoxides is even more interesting as regards synthetic applications: it also results in alkoxide anions **5** which react with aldehydes to give unsaturated alcohols **6** (Eq. 4.4). Okabe and Sun reported a one-pot approach to the vitamin D_3 analogue involving the reaction of **2** with epoxide and aldehyde.[17b]



(4.4)

Schlosser[18,19] proposed another method of synthesis of the ylide 2. He obtained ylide **2** by reaction of the *C*-bromo ylide **8** with *tert*-butyllithium in hexane at –75°C. However the spectroscopic characteristics of the ylide **2**, obtained by Schlosser, differed from those of the ylide prepared earlier by Corey[17]. Schlosser has proved by low-temperature NMR that the reaction of triphenylphosphonium methylide with alkyllithium is accompanied by *ortho* lithiation of the benzene ring and the formation of the lithiated ylide7 (Eq. 4.5)[18,19].



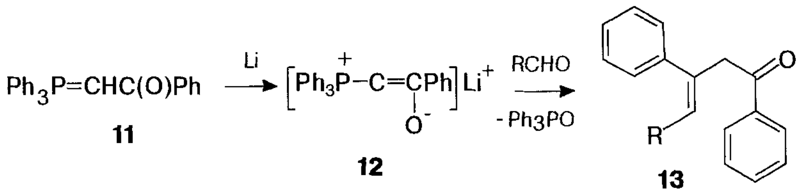
(4.5)

Later, Corey[21] published a detailed procedure for the synthesis of methylide **2** by reaction of triphenylphosphonium lithium methylide **1** with *tert*-butyllithium and demonstrated the high reactivity of the reagent in reactions with various electrophiles. Corey rationalized (although, without convincing evidence) the different spectral characteristics of the ylides prepared by the different methods by proposing the existence of a tautomeric equilibrium **2** $\rightleftharpoons$ **7**[21].

It should be noted that the 'hyperactive' *C*-lithium methylides have not found extensive synthetic application, because of the difficulties associated with their preparation. However, the metallated ylides **10** are relatively readily formed from the stabilized phosphorus ylides **9** with electron-withdrawing substituents on the α carbon atom (Eq. 4.6). This method is quite frequently used to increase the reactivity of phosphorus ylides[22–27].

$$\underset{\mathbf{9}}{R_3P{=}CHR'} \xrightarrow{M} \underset{\mathbf{10}}{[R_3P{=}\bar{C}R']M^+} \qquad R{=}C(O)Ph,\ SO_2Ph,\ CN;\ M{=}Li,\ Na,\ K \qquad (4.6)$$

For example, although triphenylphosphonium phenacylide **11** reacts with aldehydes with difficulty and does not react with ketones, the highly reactive ylide **12**, formed by reaction of **11** with lithium in HMPTA–benzene, alkenates aldehydes and ketones to give the enone **13** (Eq. 4.7)[22,23].

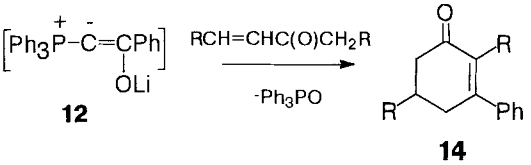


(4.7)

The Wittig reaction of the lithium derivative 12 (Eq. 4.7)

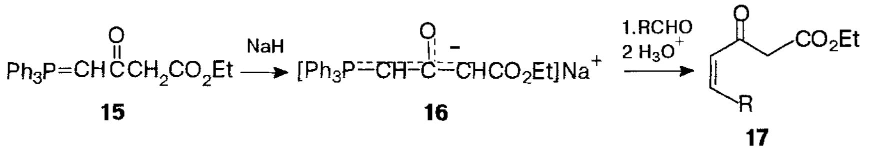
A solution of HMFTA (distilled from calcium hydride), benzene (150 mL), and triphenylphosphonium phenacylide (15.2 g, 0.04 mol) were placed in a three-necked round-bottomed flask. Lithium (0.04 mol) was then added in small pieces and the reaction mixture was stirred at room temperature. A slight increase in temperature and the red color of the reaction mixture were observed during reaction. All the lithium dissolved within 3–4 h. A ketone (0.04 mol) was then added and the colorless mixture was heated under reflux overnight. The reaction solution was mixed with ice water. The organic layer was separated and the aqueous layer was extracted with benzene. The benzene extracts were washed with water, dried over $CaCl_2$, and evaporated under vacuum. The residue was chromatographed (with benzene as eluent) to separate of the triphenylphosphine oxide. The solvent was removed under reduced pressure and the residue was distilled in vacuum to collect the fraction corresponding to vinylketone.

Lithium ylide **12** reacts with α,β-unsaturated ketones by Michael addition thus giving rise to the substituted cyclohexanone **14** (Eq. 4.8)[23,24]:



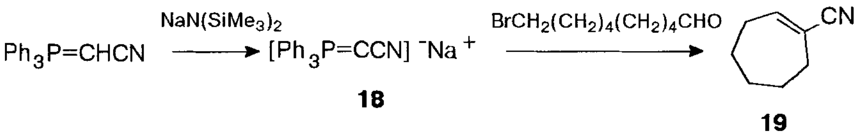
(4.8)

The stabilized ylide **15** has low reactivity towards aldehydes whereas its sodium derivative **16** readily enters into the Wittig reaction with carbonyl compounds to give the conjugated unsaturated β-oxoesters **17** with the *Z* configuration (Eq. 4.9)[25,26]:



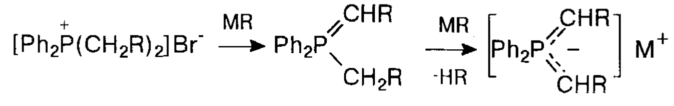
(4.9)

Sodium derivatives of triphenylphosphonium cyanomethylide **18** were synthesized by Bestmann and Schmidt[27] for the preparation of cyclic compounds, *e.g.* **19** (Eq. 4.10):



(4.10)

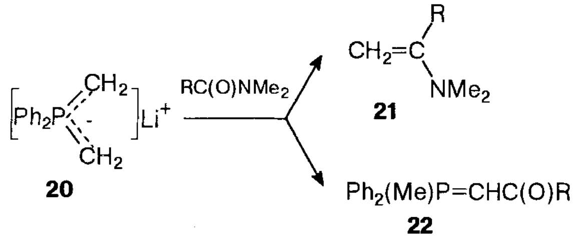
α–Carbon metallated ylide carbanions **20**, which can be obtained by direct addition of 2 equiv. of a base to a phosphonium salt or of 1 equiv. of base to a phosphorus ylide, have recently found an important synthetic application. Some ylide carbanions **20** were isolated in the form of crystalline (colorless or colored) compounds and highly reactive *tris* carbanions were obtained by reaction of trialkylphosphonium ylides with excess butyllithium[14,27-37]. The structures of the ylide carbanions **20** were determined by X-ray crystallography[38,39] and NMR spectroscopy[40] (Eq. 4.11):



(4.11)

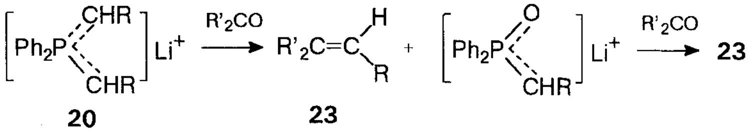
M=Li, Na, K; MR=KH, NaH, $NaNH_2$, LiAlk **20**

Ylide anions can serve as the starting material for the synthesis of other C-substituted phosphorus ylides, because the metal atoms in them are readily substituted by various groups in reactions with electrophiles[41]. Some examples of such syntheses are given in this review. Ylide anions react even with electrophiles, which do not react, or react with difficulty, with other phosphorus ylides. For instance, they alkenate carboxyamides to give enamines **21** or acyl ylides **22**, depending on the reaction conditions. Analogously, the reaction of the ylide anions **20** with carboxylic ester ylides yields vinyl ethers or acyl ylides (Scheme 4.1)[14]:



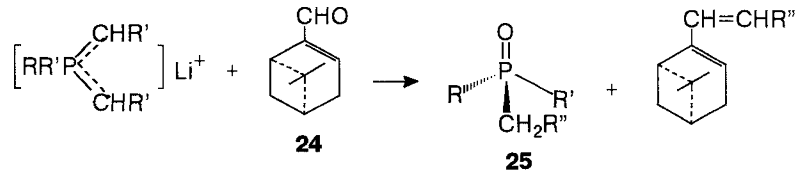
Scheme 4.1

The reactivity of ylide anions **20** is no inferior to that of 'hyperactive' *C*-lithium methylides **2** synthesized by Corey and Schlosser, and they are considerably superior in availability and stability. Thus, ylide anions **20** (R = H)[41–52] react at room temperature with sterically hindered ketones (e.g. di-*tert*-butyl ketone and fenchone), which cannot be alkenated by triphenylphosphonium methylide. Because the ratio of ylide anion **20** to the carbonyl compound in this reaction is 1:2, the yields of alkenes **23** can reach 180–200% relative to the phosphorus ylide (Eq. 4.12)[50]:



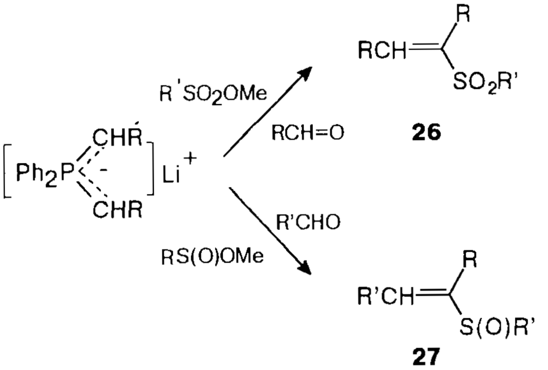
(4.12)

Reaction of ylide anions with chiral aldehydes **24** is accompanied by asymmetric induction, which results in optically active tertiary phosphine oxides **25** (Eq. 4.13)[14]:



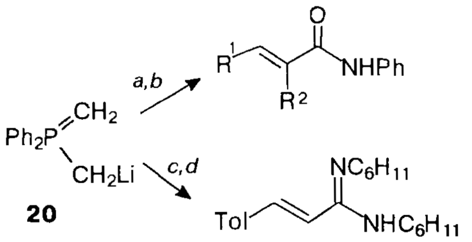
(4.13)

Reactions of ylide anions with aldehydes, carbonates, thiocarbonates, isocyanates, carbodiimides, sulfinates, and sulfinates have been documented[42–53]. The last two reactions give the *E* isomers of unsaturated sulfones and sulfoxides **26** and **27** (Scheme 4.2)[49,51]:



Scheme 4.2

Cristau and coworkers[51b] have studied the reactivity of ylide anions **20** toward carbodiimides and isocyanates (Scheme 4.3).



a= PhNCO; b= $R^1R^2C=O$;

c= $C_6H_{11}N=C=NC_6H_{11}$, d=TolCHO

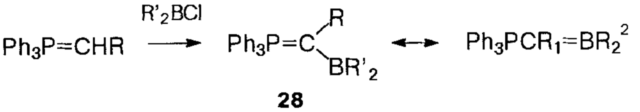
Scheme 4.3

The reaction is performed in two steps: heterocumulene is first treated with the ylide anion and then the ylide adduct is added to the reaction mixture with an aldehyde or ketone. As a result α,β-unsaturated amides and amidines are formed in high yields and stereoselectivity.

Free ylides with Group II metals (beryllium, magnesium) on the *a* carbon atom have not yet been obtained. According to the quantum-chemical calculations the molecule of the simplest ylide, $H_3P=CHBeH$, has planar structure[16].

4.2.2 Ylides Containing Group IIIA Elements

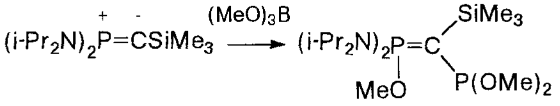
Compounds of group IIIA elements of the periodic table are strong Lewis acids and readily react with phosphorus ylides[54 58]. Reactions of triphenylphosphonium alkylides and benzylides with dialkylchloroboranes in benzene are accompanied by transylidation and result in α-dialkylboryl-substituted ylides **28**, which were isolated in the crystalline form (Eq. 4.14). The NMR spectra of ylides **28** are indicative of a mesomeric structure[58–60]. Phosphorus ylides react with alkyldichloroboranes to give bis(ylidyl)alkylboranes.



$$Ph_3P{=}CHR \xrightarrow{R'_2BCl} Ph_3P{=}C(R)BR'_2 \longleftrightarrow Ph_3PCR_1{=}BR_2{}^2 \qquad (4.14)$$

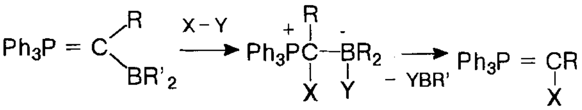
28

The C-boron substituted ylide **30** was isolated by Bertrand and coworkers[61] by addition of trimethyl borate to phosphinecarbene **29** (Eq. 4.15):



$$(i\text{-}Pr_2N)_2\overset{+}{P}{=}\overset{-}{C}SiMe_3 \xrightarrow{(MeO)_3B} (i\text{-}Pr_2N)_2P(OMe){=}C(SiMe_3)P(OMe)_2 \qquad (4.15)$$

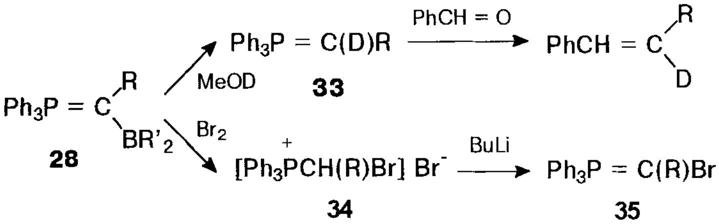
C-Boron substituted ylides **28** are characterized by high reactivity. They readily react with polar compounds X–Y to give ylides **32** and boranes via the intermediate onium complexes **31** (Eq. 4.16):



$$Ph_3P{=}C(R)BR'_2 \xrightarrow{X-Y} Ph_3\overset{+}{P}(X)\text{–}C(R)\text{–}\overset{-}{B}R_2(Y) \xrightarrow{-\,YBR'} Ph_3P{=}C(R)X \qquad (4.16)$$

28 **31** **32**

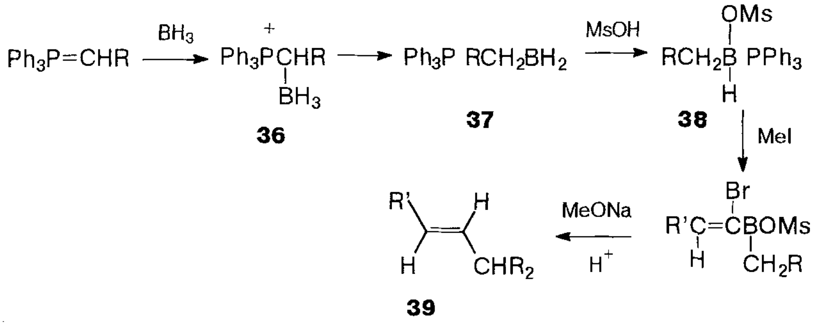
Reaction of the ylide **28** (R = Alk) with deuteromethanol gives deuterated ylides **33** which have been used for the preparation of deuterated olefins (Scheme 4.4). The phosphonium salts **34** were obtained by reaction with bromine; when treated with butyllithium, they yield C-bromo-substituted phosphorus ylides **35** (Scheme 4.4)[60].



Scheme 4.4

Bestmann and coworkers[57,62] have developed a stereoselective method for synthesis of *E* olefins, in particular pheromones, based on products of hydroboration of phosphorus ylides. The key step in the synthesis is the reaction of a phosphorus ylide with borane. The betaine **36** thus formed undergoes rearrangement into the adduct of monoalkylborane with triphenyl-phosphine **37**. The latter is converted to *E* olefin **39** with 99% stereochemical purity by a series of successive reactions. (Scheme 4.5).

Attempts to synthesize phosphorus ylides with aluminum, gallium, indium, and thallium on the *a* carbon atom have failed. These ylides are unstable and are rapidly converted into dimers and oligomers with the structure of metallocycles[1,3,63–65].



Scheme 4.5

4.2.3 Ylides Containing Group IVA Elements

C-Silyl-substituted phosphorus ylides are of considerable preparative importance. The interest in these compounds is because of their availability, stability, and high reactivity. C-Germanium- and C-tin-substituted phosphorus ylides have been studied less.

Reactions of simple phosphorus ylides containing hydrogen atoms on the α carbon atom with silicon, germanium, and tin halides (at a 2:1 ratio of the reagents) are most often used for synthesis of C-substituted phosphorus ylides **40** (Eq. 4.17)[66,67]. There have been numerous reports of the synthesis of cyclic and acyclic C-silyl-substituted phosphorus ylides by this method (Eq. 4.18)[1,66–73].

$$R_3P = CH_2 \xrightarrow{R'_3MCl} [R_3PCH_2MR'_3]^+Cl^- \xrightarrow[-[R_3PMe]^+\,Cl^-]{R_3P\,=\,CH_2} \underset{\mathbf{40}}{R_3P = CHMR'} \tag{4.17}$$

$$2Ph_3P{=}CH_2 \xrightarrow[-[Ph_3PMe]X^-]{Me_3SiX} Ph_3P{=}CHSiMe_3 \xrightarrow[-[Ph_3PMe]X^-]{Me_3SiX/Ph_3P{=}CH_2} Ph_3P{=}C(SiMe_3)_2 \tag{4.18}$$

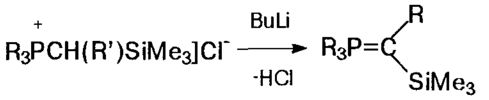
Triphenylphosphonium bis(trimethylsilyl)methylide (Eq. 4.18, X = Br)[67a–c]

A solution of triphenylphosphonium methylide (18 g, 0.065 mol) in toluene (150 mL) was placed in a 250-mL round-bottomed flask and a solution of freshly distilled trimethylsilyl bromide (7.3 g, 0.048 mol) was added with stirring. The reaction mixture was stirred under argon at room temperature for 12 h, and at 100°C for 2h. The mixture was filtered and the separated solid was washed with ether and the solvent was removed under reduced pressure. Acetonitrile (~40 mL) was added to the residue and the solution was placed in a freezer overnight. The desired product was separated by filtration and dried under vacuum. Yield 6 g (65%).

Reactions of carbanions **41** with silicon, germanium, tin, and lead halides in 1:1 ratio lead to the formation of C-mono- or C-dimetal-substituted phosphorus ylides **42** in high yields, which enables more economical use of the initial phosphorus ylides (Eq. 4.19)[74–77].

$$\underset{\substack{\mathbf{41}\\ \mathrm{M=Ge,\ Si,\ Sn,\ Pb}}}{[\mathrm{Me}\overset{+}{\mathrm{P}}(\mathrm{CH}^-_2)_3]2\mathrm{Li}^+} \xrightarrow{\mathrm{Me_3MCl}} \underset{\mathbf{42}}{\mathrm{Me_3P{=}C(MMe_3)_2}} \qquad (4.19)$$

C-silyl-substituted ylides are often prepared by treating the corresponding phosphonium salts with organolithium compounds (Eq. 4.20)[66–78]:



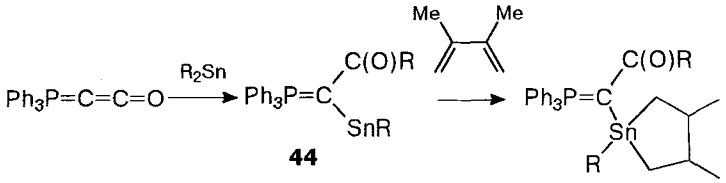
(4.20)

The reaction of trimethylphosphonium trimethylsilylmethylide with heterosiloxanes provides a simple and convenient route to germanium-, tin- and lead-containing ylides **43**. The driving force of this reaction is the formation of disiloxane (Eq. 4.21)[74,79]:

$$\mathrm{Me_3P{=}CHSiMe_3} \xrightarrow[\mathrm{(Me_3Si)_2O}]{\mathrm{Me_3SiOMMe_3}} \underset{\mathbf{43}}{\mathrm{Me_3P{=}CHMMe_3}} \qquad (4.21)$$

Silicon-containing phosphorus ylides can also be prepared by reaction of phosphorus alkylides with silacyclobutane derivatives as a result of the insertion of the ylide carbon atom into the Si–C bond[80–82].

Ketene ylides add the derivatives of two-coordinate tin, and are converted into ylides **44** in high yields. The latter readily enter into [1+4]-cycloaddition reactions with dienes to form C-tin-substituted ylides **45** (Eq. 4.22)[83]:



45

(4.22)

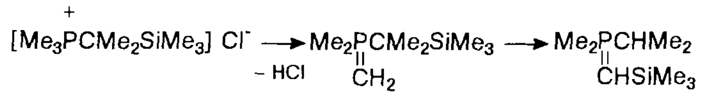
Phosphorus ylides stabilized by silicon, germanium, and tin atoms are thermally stable and can be purified by distillation in vacuo or crystallization from organic solvents.

Silicon atoms on the ylide carbon atom reduce the basicity and nucleophilicity of the corresponding phosphorus ylides by stabilizing the carbanion, which follows, for instance, from transylidation[66,78–82,84]. The stabilizing effect of the silicon atom was previously attributed to the participation of d-orbitals in the delocalization of the negative charge on the ylide carbon atom[1,52,66,78]. At present, however, the concept of electrostatic interaction and charge redistribution on the ylide carbon atom is more popular. It has been suggested that increasing the space around the carbanion center and the corresponding decrease in the repulsion between the high electron density on the ylide carbon atom and the valence shell bonding electrons of the elements of the third period should be considered[85]. The interaction between the phosphorus atom and the ylide carbon atom is regarded as negative hyperconjugation, which results in a shift of electron density from the occupied p-orbital of the ylide carbanion to the vacant s-orbital of the phosphorus ligand. In this case, the role of the d-orbitals of the heteroatom is reduced to a polarization function[86]. This point of view is supported by physicochemical studies and quantum-chemical calculations[1,52,66,87–91].

Trimethylsilyl groups on the ylide carbon atom are characterized by high mobility and in this sense might be regarded as analogs of the proton. C-silicon-substituted phosphorus ylides can be readily desilylated by reaction with hydroxyl compounds, e.g. alcohols; this is a convenient method for the preparation of ylides **46** in high purity (Eq. 4.23)[74]:

$$\underset{\mathrm{R = Alk,\ Ph}}{\mathrm{R_3P = CHSiMe_3}} \xrightarrow{\mathrm{MeOH}} \underset{\mathbf{46}}{\mathrm{R_3P = CH_2}} + \mathrm{MeOSiMe_3} \qquad (4.23)$$

Silyl groups on C-silylated ylides migrate to other carbanionic centers of the molecule, thus reducing their nucleophilicity; this confirms the validity of the comparison of silyl groups on the ylide carbon atom with the proton (Eq. 4.24)[74]. The migration of the silyl groups of silylated ylides can occur by both intramolecular and intermolecular (disproportionation) processes (Eq. 4.25)[66,74,79,80].



$$[\mathrm{Me_3\overset{+}{P}CMe_2SiMe_3}]\ \mathrm{Cl^-} \xrightarrow[-\mathrm{HCl}]{} \mathrm{Me_2\underset{\underset{\displaystyle CH_2}{\|}}{P}CMe_2SiMe_3} \longrightarrow \mathrm{Me_2\underset{\underset{\displaystyle CHSiMe_3}{\|}}{P}CHMe_2} \qquad (4.24)$$

$$\mathrm{Me_3P{=}CH_2} + \mathrm{Me_3P{=}C(SiMe_3)_2} \longrightarrow \mathrm{2Me_3P{=}CHSiMe_3} \qquad (4.25)$$

Because Me₃Sn, Me₃Ge, and Me₃Pb groups migrate equally readily in phosphorus ylide molecules, C-monostannylsubstituted phosphorus ylides **47**, which readily disproportionate into distannylsubstituted ylides **48**[48], could not be isolated in the individual form. They were identified only by spectroscopy (Eq. 4.26)[66,74,75,79,80]:

$$2[\mathrm{Me_3\overset{+}{P}CH_2SnMe_3}]\mathrm{Cl^-} \longrightarrow \underset{\mathbf{47}}{\mathrm{2Me_3P{=}CHSnMe_3}} \xrightarrow[-\mathrm{Me_3P=CH_2}]{} \underset{\mathbf{48}}{\mathrm{Me_3P{=}C(SnMe_3)_2}} \qquad (4.26)$$

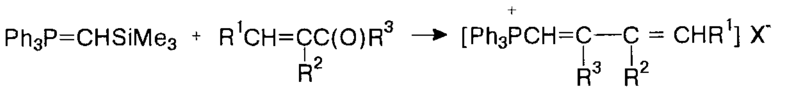
Trimethylsilyl groups on the α carbon atom in phosphorus ylide **49** can be exchanged or various substituents by reaction with chlorine-containing electrophiles (chlorophosphines, phosphorus trichloride, chloroarsines, and chlorostilbenes) to yield phosphorus-, arsenic-, and antimony-substituted ylides **50**[66,74,92–94]. Different silicon-containing heterocycles[52,67], cyclic and acyclic bifunctional ylides[54,63–65], were obtained by reaction of phosphorus ylides with chlorosilanes (Eq. 4.27):

$$\underset{\mathbf{49}}{R_3P{=}C(R')SiMe_3} \xrightarrow[-Me_3SiCl]{R''Cl} \underset{\mathbf{50}}{R_3P{=}CR'R''} \qquad (4.27)$$

C-Silyl-substituted phosphorus ylides react with carbonyl compounds both according to Wittig (route *a*) and Peterson (route *b*) pathways[56,95–97]. Because a mixture of products is usually formed, this reaction is of limited synthetic importance (Eq. 4.28):

$$RCH{=}CHSiR^2_3 \xleftarrow[R^1_3P{=}O]{a} R^1_3P{=}CHSiR^2_3 + RCHO \xrightarrow{b} [R^1_3\overset{+}{P}CH{=}CHR]R^2_3SiO^- \qquad (4.28)$$

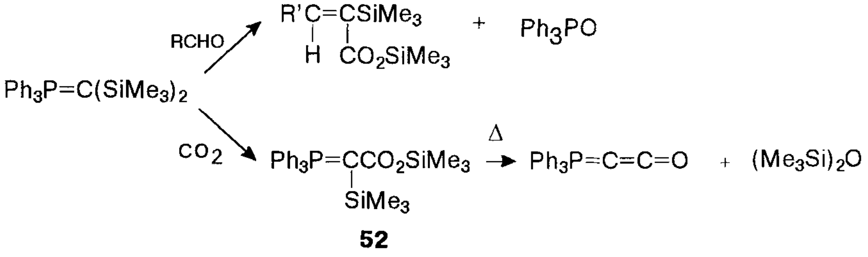
Occasionally, however, reaction of C-silyl-substituted phosphorus ylides with carbonyl compounds occurs regioselectively. Thus, triphenylphosphonium trimethylsilylmethylide reacts with unsaturated carbonyl compounds to form conjugated phosphonium salts **51** in yields of 50–100% (Eq. 4.29)[98].



$$Ph_3P{=}CHSiMe_3 + R^1CH{=}\underset{R^2}{\underset{|}{C}}C(O)R^3 \longrightarrow [Ph_3\overset{+}{P}CH{=}\underset{R^3}{\underset{|}{C}}{-}\underset{R^2}{\underset{|}{C}}{=}CHR^1]\,X^- \qquad (4.29)$$

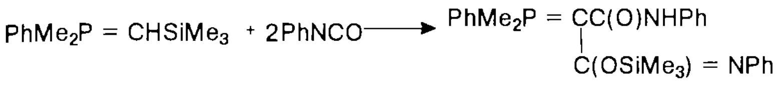
51

The reaction of bis-silylated phosphorus ylides with carbon dioxide results in silylated acyl ylides **52**, which react with aldehydes to give silyl esters of α,β-unsaturated carboxylic acids in good yields and with high stereoselectivity. Thermolysis of ylides **52** results in ketene ylides (Scheme 4.6)[99,100].



Scheme 4.6

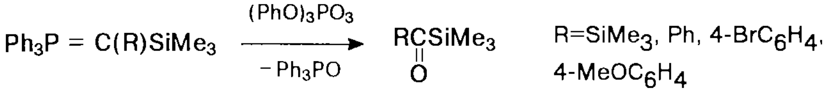
Silylated phosphorus ylides give adducts with isocyanates 53[99], isothiocyanates, and carbon disulfide (Eq. 4.30):



$$PhMe_2P=CHSiMe_3 + 2PhNCO \longrightarrow PhMe_2P=\underset{\displaystyle C(OSiMe_3)=NPh}{\underset{|}{C}}C(O)NHPh \qquad (4.30)$$

53

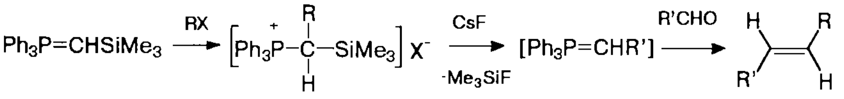
The acyl silanes 54 were obtained by oxidation of silylated ylides with the triphenyl phosphite–ozone adduct (Eq. 4.31)[101-103]:



$$Ph_3P=C(R)SiMe_3 \xrightarrow[-Ph_3PO]{(PhO)_3PO_3} R\underset{\underset{\displaystyle O}{\|}}{C}SiMe_3 \qquad R=SiMe_3, Ph, 4\text{-}BrC_6H_4, 4\text{-}MeOC_6H_4 \qquad (4.31)$$

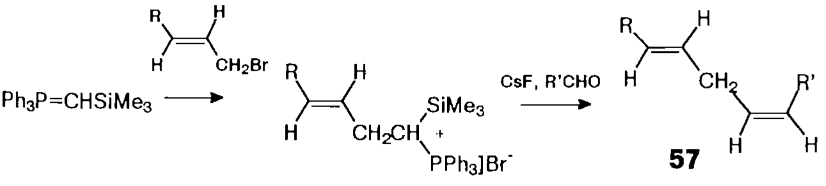
54

C-Silyl-substituted ylides are highly nucleophilic in reactions with alkyl halides. The α-silyl-substituted phosphonium salts thus formed undergo smooth cleavage under the action of cesium fluoride with the formation of new phosphorus ylides[104-108]. This reaction has served as the basis for the development of convenient methods for the synthesis of diverse natural compounds, including homoconjugated pheromones[105-108]. For example, reaction of triphenylphosphonium trimethylsilylmethylide with alkyl halides results in C-silyl-substituted phosphonium salts, 55, which are converted into *Z* alkenes, 56, on elimination of trimethylsilyl fluoride in reactions with cesium fluoride in the presence of aldehydes (Eq. 4.32)[95,101]:



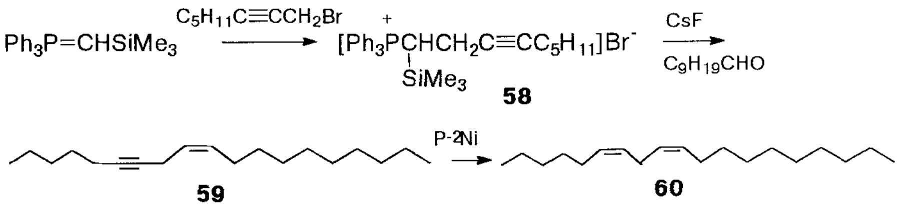
55 **56** (4.32)

Alkylation of C-silyl-substituted ylides with allylic bromides has been used to prepare *Z,E* dienes 57 (Eq. 4.33)[100]:



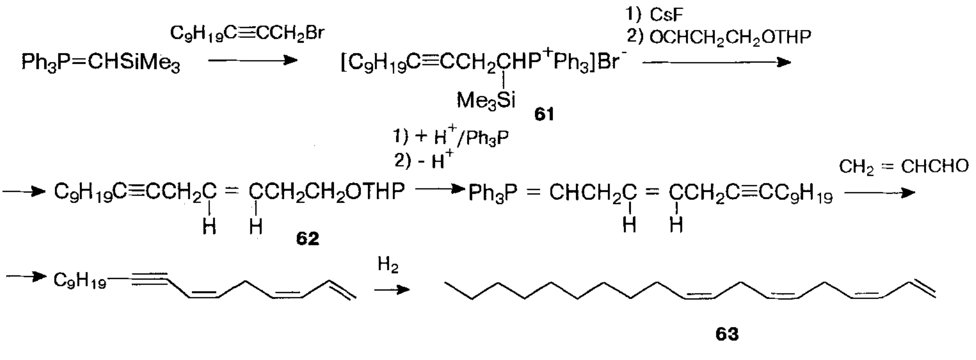
57 (4.33)

The alkylation of C-silylated ylides with acetylenic alkyl halides and subsequent desilylation of the phosphonium salts formed 58 by cesium fluoride in the presence of an aldehyde produces enynes 59 with a 98% *Z* stereoselectivity. Reduction of the latter with P-2 nickel leads to *Z,Z* dienes **60** containing C=C bonds separated by a methylene group (Scheme 4.7)[100]: By use of this reaction, Bestmann and coworkers[109,110] obtained *Lepidoptera* pheromones, in particular *Z,Z*-nonadeca-6,9-diene, a component of the *Bupalus piniarius* pheromone complex.



Scheme 4.7

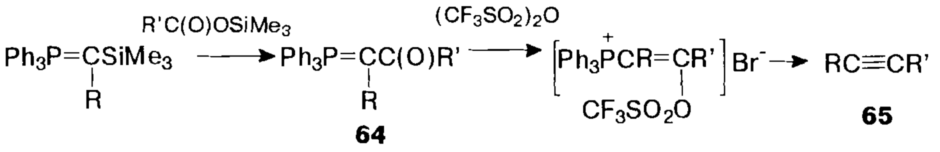
The silyl-containing phosphonium salt **61** was obtained by alkylation of triphenylphosphonium trimethylsilylmethylide by 1-bromododeca-2-yne; its desilylation by cesium fluoride in the presence of the aldehyde resulted in the enyne **62**. The latter was converted into tetraene **63** which is a component of *Operophtera brumata* pheromones (Scheme 4.8)[100,109].



Scheme 4.8

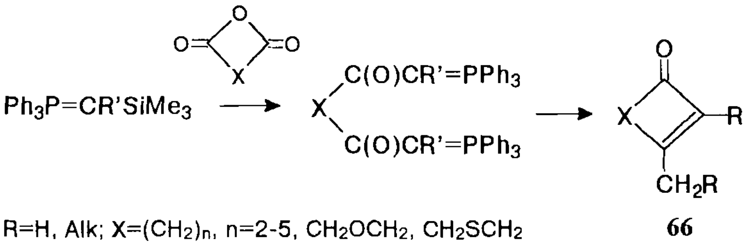
The reaction of C-silyl-substituted phosphorus ylides with trimethylsilyl carboxylates is accompanied by elimination of hexamethyldisiloxane and therefore provides a convenient method for the synthesis of acyl ylides **64**. Acylylides **64** were used by Bestmann et al.[71,102,105,106,110] in the synthesis of *N-tert*-butoxycarbonyl-substituted merukatinone[111], the starting material for the preparation of medicinal compounds and 1,2-disubstituted acetylenes[104].

Synthesis of acetylenes involved the treatment of the acyl ylides **64** with trifluoromethane sulfonic anhydride; the O-substituted vinylphosphonium salts **65** formed were reduced with sodium amalgam (Eq. 4.34):



(4.34)

The reaction of C-silyl-substituted phosphorus ylides with carboxylic acids proceeds in a similar manner. Cycloalkenones **66** containing 5–8 atoms in the ring were also prepared in high yields by reaction of C-silyl-substituted phosphorus ylides with acid anhydrides (Eq. 4.35)[71]:



(4.35)

The reaction of C-silyl-substituted phosphorus ylides with silyl carboxylates has served as the basis for the development of methods for the synthesis of ceramide, leucotriene A4[111-113] components of the *Manica ribuda* ant pheromone[105].

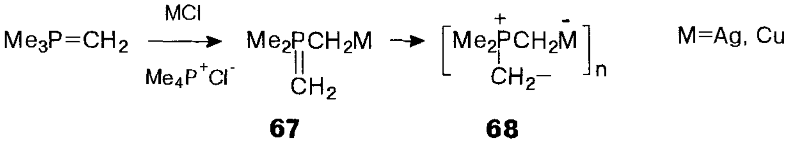
C-Silyl-substituted phosphorus ylides are used as ligands in transition metal complexes. Stable organometallic complexes with metal–carbon bonds are formed by reaction of C-silyl-substituted phosphorus ylides with halides of copper(I), silver, gold, and their phosphine complexes[114-116]. Neutral complexes of iron, chromium, molybdenum, and tungsten were also synthesized[117-122]. Examples of C-silyl-substituted complexes are discussed in the next section and in other reviews[1-4].

4.3 Phosphorus Ylides Substituted on the α–Carbon Atom by Transition Metal Atoms

Transition metal atoms on the ylide carbon atom substantially affect its negative charge, and consequently, the properties of the ylides. Three main mechanisms describing the interaction of transition metals with the ylide carbanion can be distinguished. Transition metals with σ-donor properties, such as mercury, increase the electron density on the ylide carbon atom and enhance the nucleophilicity of the ylides. The electron density on the α carbon atom decreases if the electronic interaction of transition metals with the ylide carbanion is of the d_π–p_π type and the metal–carbon bond acquires partially double character. The relative contribution of these two opposite effects depends on the nature of the metal atom and the surrounding ligands. Finally, transition metals can form additional coordinate bonds with the ylide carbon atoms, which can lead to dimerization or oligomerization of the organometallic complexes.

4.3.1 Ylides Containing Group IB or Group IIB Atoms

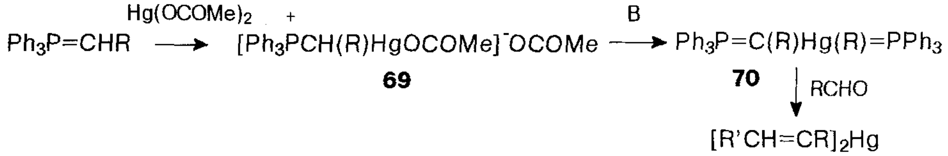
The reactions of phosphorus ylides with copper, gold, and silver halides result in the formation of ylides **67**, which are readily dimerize into linear and cyclic complexes **68** because of the high coordination number of the metal atoms (Eq. 4.36)[115,116,123–125].



$$Me_3P{=}CH_2 \xrightarrow[Me_4P^+Cl^-]{MCl} \underset{\underset{CH_2}{\|}}{Me_2PCH_2M} \longrightarrow \left[\underset{\underset{CH_2-}{|}}{Me_2\overset{+}{P}CH_2\overset{-}{M}}\right]_n \qquad M{=}Ag,\ Cu \qquad (4.36)$$

67 **68**

It was, therefore, impossible to isolate true ylides of the type **67**. In contrast, C-mercury-substituted phosphorus ylides are monomers. As has already been mentioned, mercury atoms increase electron density on the ylide carbon because of their σ-donor properties. It is, therefore, necessary that a second substituent on the *a* carbon atom should compensate for the electron-donating effect of the metal atom to stabilize mercurated ylides. Benzoyl, cyano-, or methoxycarbonyl groups can serve as such substituents. For instance, phosphorus ylides $Ph_3P{=}CHR^1$ add mercuric acetate (or chloride) to form compounds **69**; their subsequent reaction with liquid ammonia or sodium methoxide leads to the C-mercurated phosphorus ylides **70**, which enter into the Wittig reaction with aldehydes (Scheme 4.9)[126,127]:

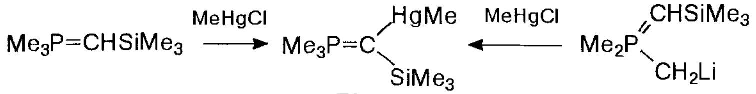


$$Ph_3P{=}CHR \xrightarrow{Hg(OCOMe)_2} \underset{\mathbf{69}}{[Ph_3PCH(R)HgOCOMe]^{+}\,{}^{-}OCOMe} \xrightarrow{B} \underset{\mathbf{70}}{Ph_3P{=}C(R)Hg(R){=}PPh_3} \xrightarrow{RCHO} [R'CH{=}CR]_2Hg$$

B=NaOMe/MOH; NH$_3$; R=CN, COPh, CO$_2$Me

Scheme 4.9

C-mercurated ylides **71** were obtained by reaction of methylmercury chloride with excess C-silylated phosphorus ylide or its anion. The ylides **71** are stable liquids, which can be distilled in vacuo (Eq. 4.37)[128].

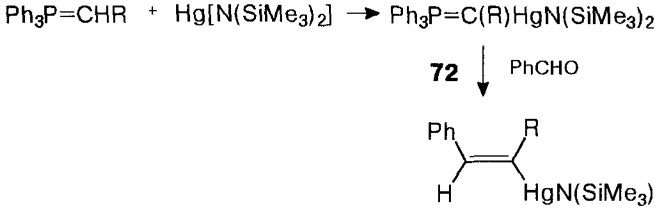


71

(4.37)

The C-mercury-substituted ylides **72**, which readily enter into the Wittig reaction to form compounds **73**, were obtained by reaction of phosphorus ylides $Ph_3P{=}CHR$ with mercury hexamethyldisilazide in inert solvents (Scheme 4.10)[129]:

Other Group IIB metals, e.g. zinc and cadmium, give ylide complexes of the type: $Ph_3P\text{-}CR_2\text{-}MCl]^+Cl^-$, M = Zn, Cd (**74**).



72

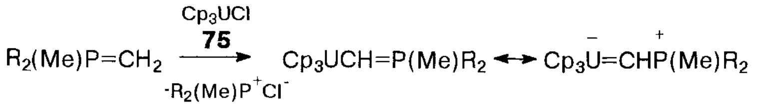
73

Scheme 4.10

Although the latter cannot be regarded as true ylides, they readily enter into the Wittig reaction and are widely used for the preparation of alkenes[130–143], for instance haloalkenes, (see Section III.3)[54,141–143].

4.3.2 Ylides Containing Atoms of the Actinide Metals

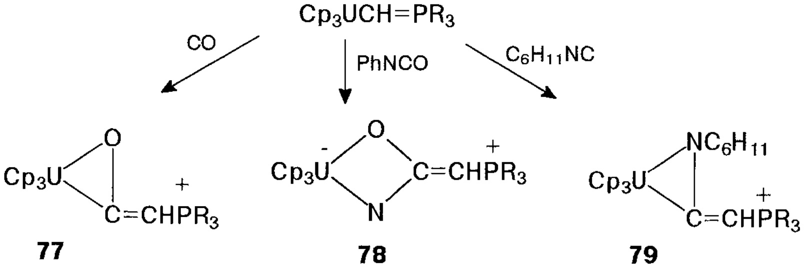
The uranium complex Cp_3UCl **75** readily undergoes transylidation under the action of phosphorus ylides and their lithium derivatives to form pyrophoric, green crystalline complexes sensitive to moisture and atmospheric oxygen. On the basis of X-ray[144–146] and electron diffraction[147] data, the metallocene ylide structure **76** was ascribed to these compounds. Shortening of the U–C and C–P bonds indicates the delocalization of the negative charge in the U–C–P fragment (Eq. 4.38)[145,147].



$$R_2(Me)P{=}CH_2 \xrightarrow[-R_2(Me)P^+Cl^-]{Cp_3UCl\ \mathbf{75}} Cp_3UCH{=}P(Me)R_2 \longleftrightarrow Cp_3\overset{-}{U}{=}CH\overset{+}{P}(Me)R_2 \qquad (4.38)$$

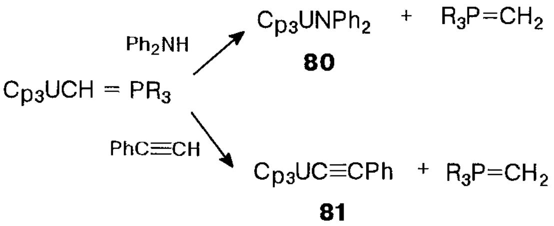
R=Me (a), Ph (b) **76a,b**

The metallocene ylides have nucleophilic properties in reactions with polar unsaturated compounds and furnish organometallic complexes **77–79**[146]. Insertion reactions into the metal–carbon bond are characteristic of uranocene ylides (Scheme 4.11)[148]:



Scheme 4.11

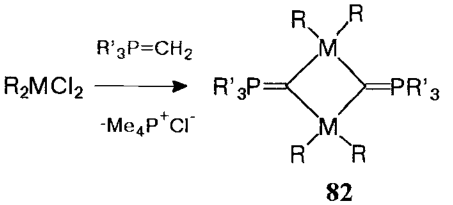
The uranocene ylides enter into metathesis reactions with compounds containing active hydrogen atoms (Scheme 4.12)[149,150]:



Scheme 4.12

4.3.3 Ylides Containing Group IVB Metal Atoms

The Group IVB transition metals (titanium, zirconium, and hafnium) stabilize the ylide carbanion as do the non-transition elements of this group, silicon and tin. Therefore, the preparation procedures, structures, and properties of phosphorus ylides, which contain metal atoms of Groups IVA and IVB on the ylide carbon atom, are similar. For instance, the four-membered cyclic bis-ylides **82** containing titanium or zirconium atoms on the ylide carbon atom are obtained in the same way as cyclic silyl-substituted phosphorus ylides. X-ray crystallographic study of phosphorus ylides **82** has shown that they have a centrosymmetric structure (Eq. 4.39)[116,151,152]:

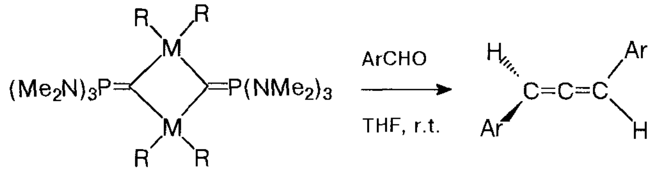


82

R= Me2N, Cl, Et;
R'= Me, Et2N, (CH2)2PMe2;
M= Ti, Zr

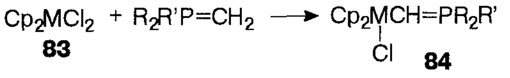
(4.39)

The titanium-containing cyclic ylides enter into the Wittig reaction with aromatic aldehydes to form the corresponding 1,3-diarylallenes; this is a promising means of their synthesis (Eq. 4.40)[153]:



(4.40)

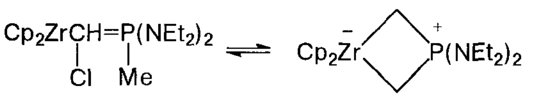
Transylidation of bis(cyclopentadienyl)titanium, -zirconium, and -hafnium dihalides **83** with phosphorus ylides results in C-metallated ylides **84** with halogen on the metal atom and special chemical properties (Eq. 4.41)[154–160].



$$\underset{\mathbf{83}}{Cp_2MCl_2} + R_2R'P{=}CH_2 \longrightarrow \underset{\mathbf{84}}{Cp_2\underset{Cl}{M}CH{=}PR_2R'}$$

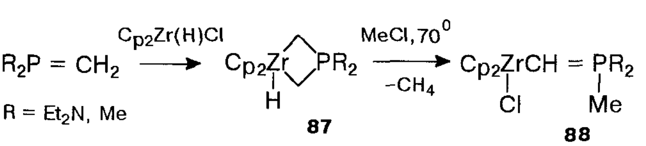
M=Ti, Zr, Hf (4.41)

For example, the zirconocene ylide **85** exists in a ring–chain, prototropic tautomeric equilibrium with the chelate complex **86** (Eq. 4.41). The position of the tautomeric equilibrium depends on the nature of the solvent (Eq. 4.42)[156]:



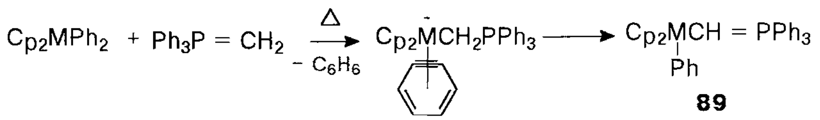
(4.42)

A zirconium hydride complex reacts with trimethylphosphonium methylide to give a four-membered cyclic ylide **88** on heating with methyl chloride (Eq. 4.43)[156–158]:



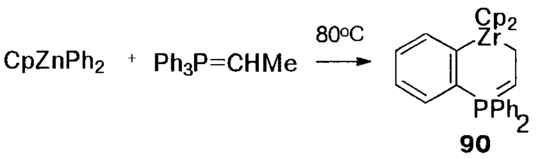
(4.43)

The metallocene ylides of titanium, zirconium, and hafnium **89** are formed by reaction of triphenylphosphonium methylide with the thermally generated (η^2-ethene)- and (η^2-aryne)metallocenes (Eq. 4.44). These reactions are accompanied by the replacement of the aryne ligand by phosphorus ylide and by a proton shift from the ylide methylene to the aryne ligand[159,160]. When bicyclopentadienyl diphenylzirconium was heated with triphenylphosphonium ethylide, the cyclic metallocene ylide **90** was formed as a result of *ortho*-metallation of the benzene ring (Eq. 4.45)[161,162]:



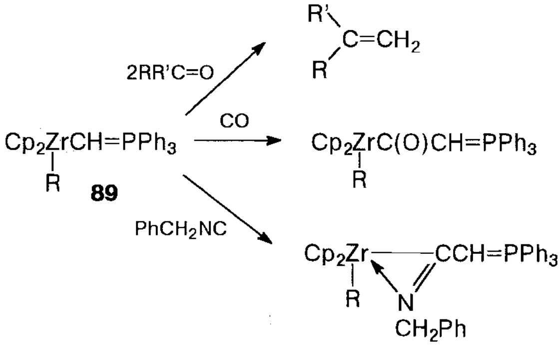
(4.44)

M=Ti, Zr, Hf



(4.45)

Although their nucleophilicity is reduced by the high electron-acceptor ability of the transition metals[161], metallocene ylides **89** react with ketones[125]. Carbon monoxide and isocyanides are readily inserted into the zirconium-carbon bond of ylides **89** (Scheme 4.13)[160–165]:



Scheme 4.13

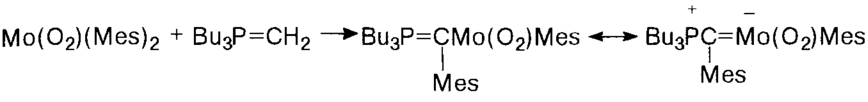
4.3.4 Ylides Containing Group VIB-VIIIB Metal Atoms

Phosphorus ylides containing atoms of Group VI–VIII transition metals are characterized by high stability on storage and the tendency to exist in a free, non-associated form. Recent detailed studies of the phosphorus-ylide complexes of Group VI–VIII transition metals has enabled the development of convenient procedures for their synthesis. The simplest method involves the substitution of ligands in the transition metal complexes by the phosphorus-ylide ligand[158,166–174]. For instance, bromopentacarbonyl complexes of manganese and rhenium undergo transylidation with phosphorus ylides to give the C-metal-substituted phosphorus ylides **91** (Eq. 4.46)[158,166]:

$$2R_3P{=}CH_2 + (CO)_5MBr \longrightarrow \underset{\mathbf{91}}{R_3P{=}CHM(CO)_5} + [R_3\overset{+}{P}Me]Br^- \qquad (4.46)$$

M=Mn, Re

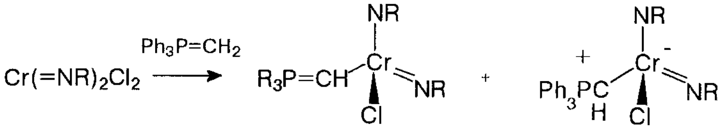
The dioxomolybdenum ylide **93** was synthesized by the reaction of the dioxomolybdenum complex **92** with tributylphosphonium methylide (Eq. 4.47)[168,169]:



$$\mathrm{Mo(O_2)(Mes)_2 + Bu_3P{=}CH_2 \longrightarrow Bu_3P{=}\underset{Mes}{C}Mo(O_2)Mes \longleftrightarrow Bu_3\overset{+}{P}\overset{-}{\underset{Mes}{C}}{=}Mo(O_2)Mes} \quad (4.47)$$

92 **93**

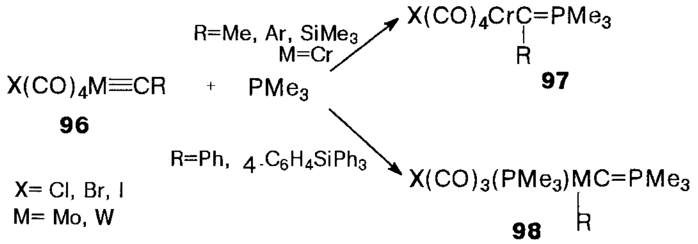
The first complex of hexavalent chromium **94**, which has high reactivity, was synthesized by transylidation of a bisalkylimide chromium complex with 2 equiv. triphenylphosphonium methylide (Eq. 4.48)[170]:



94

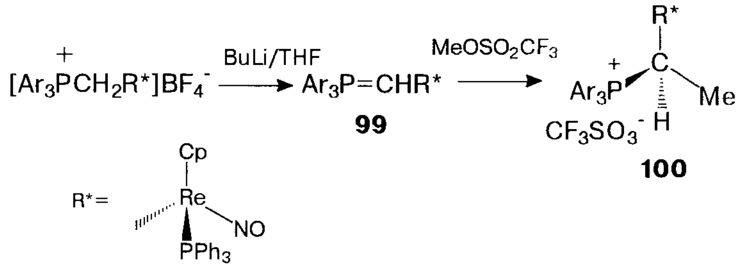
(4.48)

The phosphorus ylide **95** was synthesized by addition of trimethylphosphine to a cationic rhenium complex. The bond between the rhenium atom and the ylide carbon atom in compound **95** is shortened as a result of the presence of the transition metal (Scheme 4.14)[171-178]:



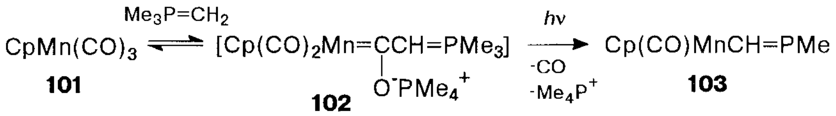
Scheme 4.14

Tertiary phosphines add to chromium, molybdenum, and tungsten carbine complexes, even at –60°C, to form stable metal-substituted phosphorus ylides **97** and **98**[171,172]. Phosphorus ylides with Group VI–VIII elements on the α carbon atom can be obtained by the salt method[173]. This method has been used to prepare optically active phosphorus ylides **99** with a chiral rhenium atom, their treatment with methyl triflate in THF at –78°C produced the *S,S,R,R*-α-rhenium-substituted phosphonium salt **100**[166] as a result of asymmetric induction on the a carbon atom (Eq. 4.49):



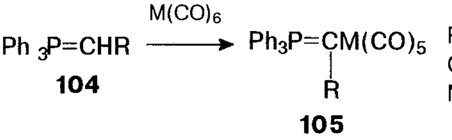
(4.49)

The manganese complex **101** reacts with trimethylphosphonium methylide to give the mesomeric, anionic manganese-substituted phosphorus ylide **102** as the adduct which is in equilibrium with carbon monoxide and results in a neutral ylide **103** with a manganese atom on the α carbon atom (Eq. 4.50)[180–183]:



$$\underset{\mathbf{101}}{\mathrm{CpMn(CO)_3}} \overset{\mathrm{Me_3P{=}CH_2}}{\rightleftharpoons} \underset{\mathbf{102}}{[\mathrm{Cp(CO)_2Mn{=}\underset{\displaystyle O^-PMe_4^+}{\underset{|}{C}}CH{=}PMe_3}]} \xrightarrow[-\mathrm{CO},\ -\mathrm{Me_4P^+}]{h\nu} \underset{\mathbf{103}}{\mathrm{Cp(CO)MnCH{=}PMe}} \qquad (4.50)$$

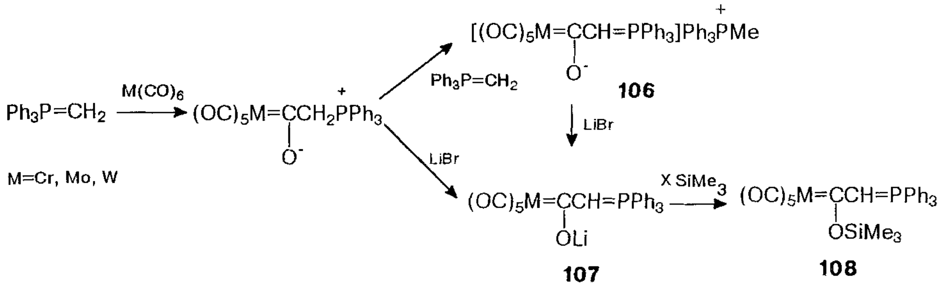
Phosphorus ylides react with the ligands of transition metal complexes to give C-metal-substituted phosphorus ylides[164–167]. For instance, when chromium, molybdenum, and tungsten hexacarbonyls were heated with ylides **104** at 50–60°C in light petroleum or were subjected to UV irradiation, complexes **105** were obtained (Eq. 4.51)[188–191]:



$$\underset{\mathbf{104}}{\mathrm{Ph_3P{=}CHR}} \xrightarrow{\mathrm{M(CO)_6}} \underset{\mathbf{105}}{\mathrm{Ph_3P{=}\underset{\displaystyle R}{\underset{|}{C}}M(CO)_5}} \qquad (4.51)$$

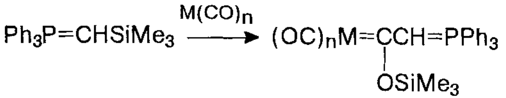
R= $\mathrm{CHC(Me){=}CH_2, CH{=}CHMe}$,
$\mathrm{CH{=}CH_2, CH{=}CHPh, CHCH{=}CH_2, Ph}$,
M= Cr, Mo, W

A large number of phosphorus ylides have been prepared that contain fragments of transition-metal complexes on the α carbon atom separated from the ylide carbanion by one or two atoms. Some of these ylides readily enter into the Wittig reaction[171]. Reaction of the phosphorus ylides with the polycarbonyls of Group VI–VIII metals can occur either by the addition of the ylide carbon atom to one of the C=O groups of the metal carbonyl or by the substitution of the C=O group. The direction of the reaction and its products depend on the reaction conditions. Thus triphenylphosphonium methylide adds to a C=O group of chromium, tungsten, and iron polycarbonyls with the formation of the stable anionic phosphorus ylides **106** with a mesomeric structure[192,193]. In the presence of lithium bromide, the phosphorus ylides **107** with a lithium atom on the enol oxygen are formed[194–196]; they are converted into the ylides **108** by reaction with trimethylsilyl triflate or fluorosulfonate (Scheme 4.15)[194]:



Scheme 4.15

The ylides **109** are also formed by reaction of metal carbonyls with C-silylated phosphorus ylides (Eq. 4.52)[197,198]:



$$Ph_3P{=}CHSiMe_3 \xrightarrow{M(CO)_n} (OC)_nM{=}C(OSiMe_3)CH{=}PPh_3 \qquad M{=}Cr,\ Mo,\ W,\ Fe;\ n{=}\ 5,6 \tag{4.52}$$

109

Hexaphenylcarbodiphorane reacts with metal carbonyl complexes with the formation of the stable and poorly reactive cumulene ylides **110** and **111** (Eq. 4.53,54)[183,196,199,200]:

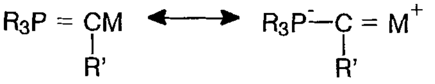
$$(CO)_5MBr \xrightarrow[-Ph_3PO]{Ph_3P=C=PPh_3} Br(CO)_4\overset{-}{M}C{\equiv}C\overset{+}{P}Ph_3 \longleftrightarrow Br(CO)_4M{=}C{=}C{=}PPh_3 \tag{4.53}$$

M=Mn, Re **110**

$$(CO)_6W + Ph_3P{=}C{=}PPh_3 \xrightarrow[-Ph_3PO]{} (CO)_5W{=}C{=}C{=}PPh_3 \tag{4.54}$$

111

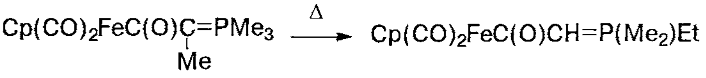
^{13}C and ^{31}P NMR spectroscopy and X-ray crystallographic structural analysis of ylides containing Group VI–VIII transition metal atoms attest to the high extent of the delocalization of the ylide carbon atom negative charge by the transition metals, which act as strong electron acceptors by a p_π–d_π mechanism. These results also indicate the considerable contribution of the resonance form with a double metal–carbon bond (Eq. 4.55)[168,169,197,198,205]:



$$R_3P = C(R')M \longleftrightarrow R_3\overset{-}{P}{-}C(R') = M^+ \tag{4.55}$$

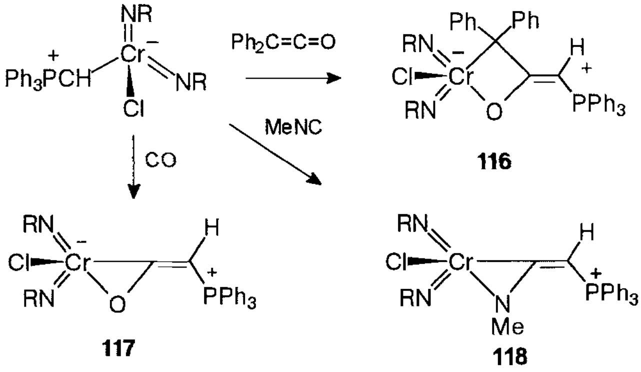
Consequently, the nucleophilicity of ylides containing transition metal atoms of the Group VI–VIII transition metal atoms is moderate, and thus they react only with strong electrophiles. X-Ray crystallographic structural analysis of compound **112** revealed the high extent of delocalization of the negative charge on the ylide carbon atom over the system of conjugated multiple bonds and the iron atom. **112** reacts at the *a* carbon atom with hydrogen chloride, trimethylchlorosilane, and alkyl halides with the formation of the phosphonium salts **113** (Eq. 4.56)[198]: The phosphorus ylides **114** rearrange on heating with the formation of new phosphorus ylides **115** (Eq. 4.57).

$$\underset{\mathbf{112}}{Cp(CO)_2FeC(O)CH{=}PR_3} \xrightarrow{R'X} \underset{\mathbf{113}}{[Cp(CO)_2FeC(O)CH(R')\overset{+}{P}R_3]\,X^-} \qquad (4.56)$$



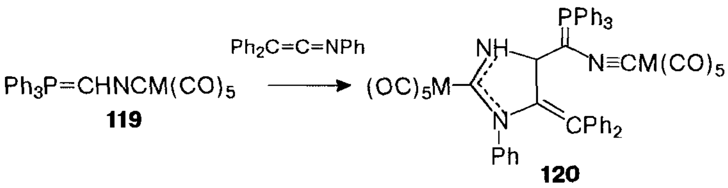
$$\underset{\mathbf{114}}{Cp(CO)_2FeC(O)\underset{Me}{C}{=}PMe_3} \xrightarrow{\Delta} \underset{\mathbf{115}}{Cp(CO)_2FeC(O)CH{=}P(Me_2)Et} \qquad (4.57)$$

Insertion reactions into the metal–carbon bond are characteristic of ylides containing the Group VI–VIII transition metals. For instance, the chromium complex **94** enters into unusual cycloaddition reactions with diphenylketene, carbon monoxide, and isocyanides with formation of vinylphosphonium salts **116–118**. (Scheme 4.16)[170]:



Scheme 4.16

The metallonitrile ylides **119**, M = Cr, W, add to ketene imine with the formation of cyclic ylides **120**[145,206]. The reaction of metallonitrile ylides with isocyanates and carbon disulfide proceeds similarly (Eq. 4.58)[207,208]:



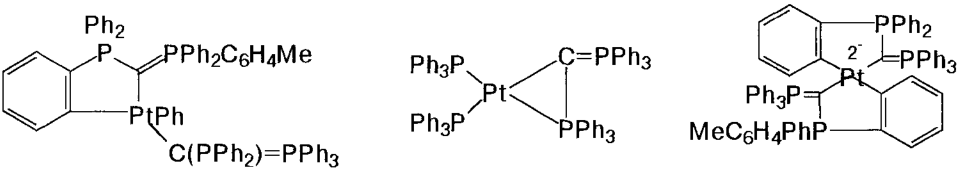
(4.58)

4.3.5 Ylides Containing Platinum Subgroup Metal Atoms

A variety of cyclic and acyclic platinum metal complexes with phosphorus ylide ligands have been synthesized. However, compounds with the double P=C bonds are rare among them, because metal-containing phosphorus ylides formed readily dimerize[37,203–206,209–212].

The compounds **121–123** were obtained from hexaphenylcarbodiphosphorane and the corresponding cationic platinum complexes and are a few examples of phosphorus ylides with platinum on the α carbon atom[3,167,213].

It follows form the above material that transition metals effectively stabilize the ylide carbanion, reducing its nucleophilicity. Nevertheless, the reactivity of such ylides is occasionally relatively high. Phosphorus ylides containing transition metals have not yet found extensive application in synthesis. Certain prerequisites enable anticipation of a considerable extension of their practical application. For instance, the metal complexes of phosphorus ylides are reported to have been used as catalysts for the polymerization of alkenes and as medicinal compounds (Scheme 4.17)[214–216]:



121 **122** **123**

Scheme 4.17

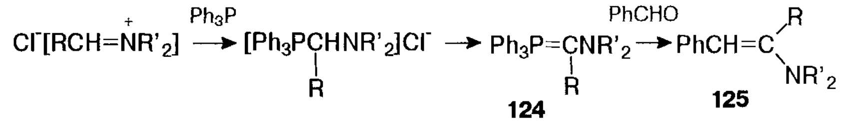
4.4 Phosphorus Ylides Substituted on the α-Carbon Atom by Atoms of Elements of Groups VA–VIIA

Phosphorus ylides substituted by Group VA-VIIA elements on the α carbon atom are of theoretical interest. They are widely used in the synthesis of biologically active compounds[9,217–220].

4.4.1 Ylides containing Group VA Elements

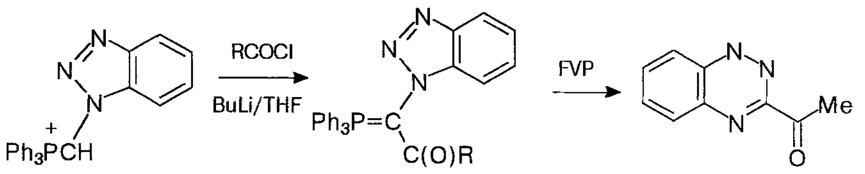
The structures of phosphorus ylides stabilized by nitrogen, phosphorus, and arsenic atoms are highly diverse because of the varying valence and different coordination states of these elements. The chemical properties of such phosphorus ylides are also characterized by considerable peculiarities. All this has promoted the development of the chemistry of this class of phosphorus ylide and elaboration on their use in new preparative methods for the synthesis of various valuable organic compounds.

Quantum-chemical *ab initio* calculations[116] show that trivalent nitrogen destabilizes the ylide carbanion. C-amino-substituted phosphorus ylides are, therefore, stable only if the second substituent on the α carbon atom has electron-accepting properties which compensate for the electron-donating effect of the amino group. For this reason transylidation cannot be used for the synthesis of C-amino-substituted ylides. The Wittig reaction of the C–N ylides **124** generated from the C-aminophosphonium salts leads to the enamines **125**. Attempts to synthesize the non-stabilized C–N ylides have failed (Eq. 4.59)[221]:



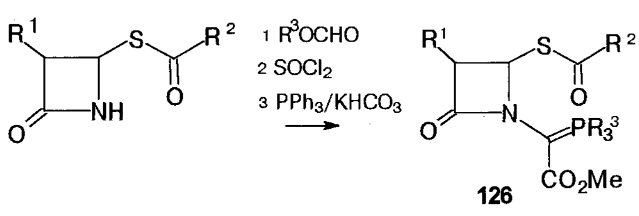
$$\mathrm{Cl^-[RCH{=}\overset{+}{N}R'_2]} \xrightarrow{\mathrm{Ph_3P}} \mathrm{[Ph_3\overset{+}{P}\underset{R}{C}HNR'_2]Cl^-} \longrightarrow \underset{\mathbf{124}}{\mathrm{Ph_3P{=}\underset{R}{C}NR'_2}} \xrightarrow{\mathrm{PhCHO}} \underset{\mathbf{125}}{\mathrm{PhCH{=}C(R)NR'_2}} \qquad (4.59)$$

The C–N ylides are usually synthesized by the dehydrohalogenation of the corresponding phosphonium salts (Eq. 4.60)[221b]:



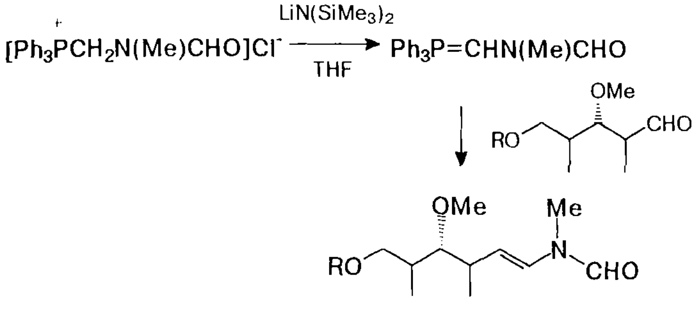
(4.60)

The methods developed by Woodward[218] for the synthesis of P–N ylides **126** containing the 4-thioacetylazetidin-2-one group on the a carbon atom, which are used for the preparation of the β-lactam antibiotics, are of considerable preparative value (Eq. 4.61)[220,221].



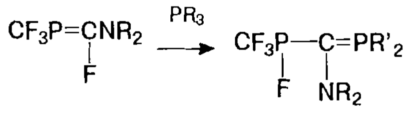
(4.61)

Paterson and coworkers[222] synthesized *N*-methylformamido-substituted phosphorus ylides by the action of lithium bis(trimethylsilyl)amide on the phosphonium salt. This ylide was shown to be an effective reagent for the transformation of aldehydes into the corresponding *N*-alkenyl-*N*-methylformamides (Scheme 4.18):



Scheme 4.18

The reaction of the compounds of two-coordinate phosphorus with lower trialkylphosphines leads to the phosphorus ylides **128**, which contain a phosphorus atom and a dialkylamino group on the α carbon atom. This reaction is accompanied by substitution of the fluorine atom on the sp^2-hybridized carbon atom with a phosphonium group and migration of the fluorine substituent to the trivalent phosphorus atom (Eq. 4.62)[223]:

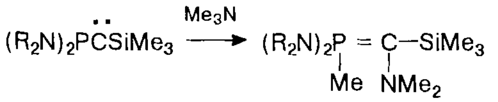


$$\mathrm{CF_3P{=}\underset{F}{\underset{|}{C}}NR_2} \xrightarrow{\mathrm{PR_3}} \mathrm{CF_3\underset{F}{\underset{|}{P}}{-}\underset{NR_2}{\underset{|}{C}}{=}PR'_2} \qquad (4.62)$$

128

R=Me, Et; R'=Me, Et

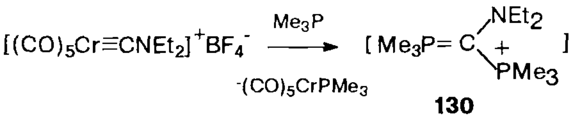
Cowley and coworkers[224] synthesized C–N phosphorus ylides **129** by adding trimethylamine to a phosphinocarbene (Eq. 4.63):



$$\mathrm{(R_2N)_2P\ddot{C}SiMe_3} \xrightarrow{\mathrm{Me_3N}} \mathrm{(R_2N)_2\underset{Me}{\underset{|}{P}} = \underset{NMe_2}{\underset{|}{C}}{-}SiMe_3} \qquad (4.63)$$

129

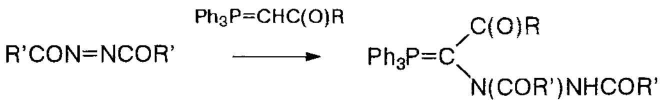
Kreissl and coworkers[225] synthesized the ylide phosphonium salt **130** by reaction of trimethylphosphine with a carbene–chromium complex (Eq. 4.64):



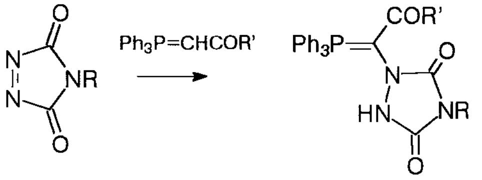
$$\mathrm{[(CO)_5Cr{\equiv}CNEt_2]^+BF_4^-} \xrightarrow[\mathrm{-(CO)_5CrPMe_3}]{\mathrm{Me_3P}} \mathrm{[Me_3P{=}C\genfrac{}{}{0pt}{}{NEt_2}{PMe_3}+\;]BF_4^-} \qquad (4.64)$$

130

The Michael addition of phosphorus ylides to acyclic (Eq. 4.65) and cyclic (Eq. 4.66) compounds with a multiple N–N bonds activated by carbonyl groups is a convenient way of synthesizing C-N ylides[226-228]:

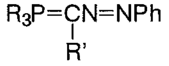


(4.65)



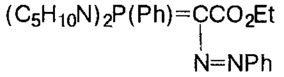
R=Alk, Ph, AlkO (4.66)

Triphenylphosphine and phosphorus acid amides react with *C*-ethoxycarbonyl- and *C*-acetyl-*N*-nitrile imines to give stable azomethylenephosphonium ylides **131** [R = Ph, $(C_5H_{10})_2N$; R′ = CO_2Et, C(O)Me]^{229,230}. The ylide **132** has been obtained by reaction of the C-carbonyl-containing ylide with diazonium salt followed by treatment with sodium ethoxide^{231}. Ylide **133** bearing two azo-groups on the *a* carbon atom was obtained by reaction of bis(phenylazo)methane with triphenyldichlorophosphorane in the presence of triethylamine^{232}:



$R_3P{=}C(R')N{=}NPh$

131



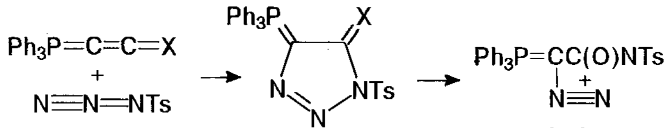
$(C_5H_{10}N)_2P(Ph){=}C(N{=}NPh)CO_2Et$

132

$Ph_3P{=}C(N{=}NPh)_2$

133

1,3-Dipolar cycloaddition of triphenylphosphonium ketene ylides to toluenesulfonyl azide leads to the ylides containing a triazoline ring; this can produce ylides **134** with a diazo group on the *a* carbon atom (Eq. 4.67)^{233}:



134

(4.67)

In contrast to the nitrogen atom, the atoms of trivalent phosphorus, arsenic, and antimony efficiently stabilize the ylide carbanion, thus making the transylidation reaction the main route to the synthesis of C-phosphino-, C-arsino-, and C-stibino-substituted phosphorus ylides^{79,80}.

C-Phosphine-substituted P-ylides **135** can be easily prepared by transylidation of simple P-ylides with chlorophosphines (Eq. 4.68, Table 4.1).

$$2Ph_3P{=}CHR + R'_2PCl \longrightarrow Ph_3P{=}C(R')PR_2 + [Ph_3PCH_2R]^+Cl^- \qquad (4.68)$$

135

Table. 4.1. C-Phosphine substituted P-ylides **135** (Eq. 4.68)

R	R'$_2$P	Ref
H	Ph$_2$P	93
Me	(C$_6$H$_{11}$)$_2$P	93
Me	Me$_2$P	79
Me	Ph$_2$P	93
Ph	Ph$_2$P	93
CO$_2$Me	Ph$_2$P	93

A convenient method for the preparation of phosphorus ylides bearing phosphorus, arsenic, or antimony atoms on the ylidic carbon atom is the reaction of C-silyl-substituted ylides with chlorophosphines, chloroarsines and chlorostilbenes, with elimination of trimethylchlorosilane. Instead of chloroarsines, arsenic trimethylsilyl ethers can be used successfully (Eq. 4.69)[79,80,154]. The reaction of lithiated trimethylphosphonium methylide with dimethylchlorostilbene leads to the formation of trimethylphosphonium dimethylstilbenomethylide in a yield of 40% (Eq. 4.70)[79,80,154]:

$$Me_3P{=}CHEMe_2 \xleftarrow[-Me_3SiCl]{Me_2ECl} Me_3P{=}CHSiMe_3 \xrightarrow[-(Me_3Si)_2O]{Me_2AsOSiMe_3} Me_3P{=}CHAsMe_2 \qquad (4.69)$$

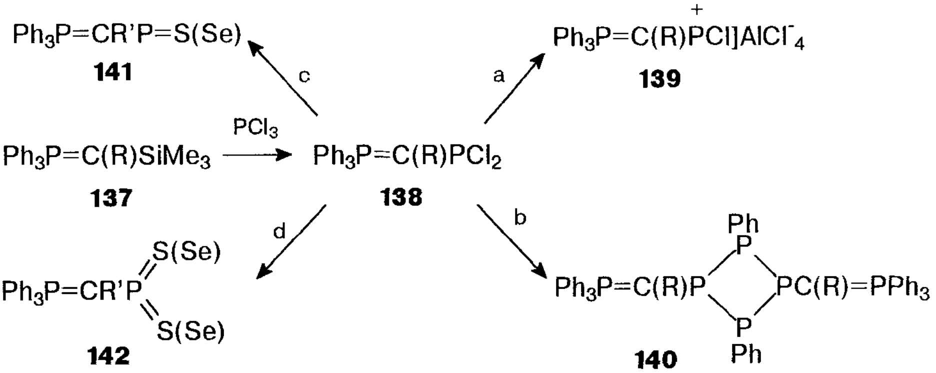
$$Me_2P(CH_2^-)_2Li^+ \xrightarrow{Me_2SbCl} Me_3P{=}CHSbMe_2 \qquad (4.70)$$

Diaryl- and dialkylchlorophosphines, alkyl- and arylchlorophosphines, aminochlorophosphines, and phosphorus trichloride react with unstabilized phosphorus ylides to give the compounds **136** with one, two, or three phosphorus ylide groups on the trivalent phosphorus atom (Eq. 4.71)[156,234-238]:

$$R_3P{=}CHR' \xrightarrow[-(3-n)\,[R_3PCH_2R]^+Cl^-]{R_nPCl_{3-n}} \underset{\mathbf{136}}{(R_3P{=}CR')_{3-n}PR_n} \quad R{=}Ph,\ Alk_2N;\ R'{=}H,\ Alk \quad n{=}0\text{-}2 \qquad (4.71)$$

In the last few years considerable attention has been paid to the synthesis of phosphorus ylides substituted on the ylide carbanion with phosphorus atoms with unusual coordination[242a,b,c,d-248]. Phosphorus ylides, containing the two-coordinate trivalent[242,248] and the three-coordinate pentavalent phosphorus atoms[243,244] on the ylide carbon atom have been synthesized.

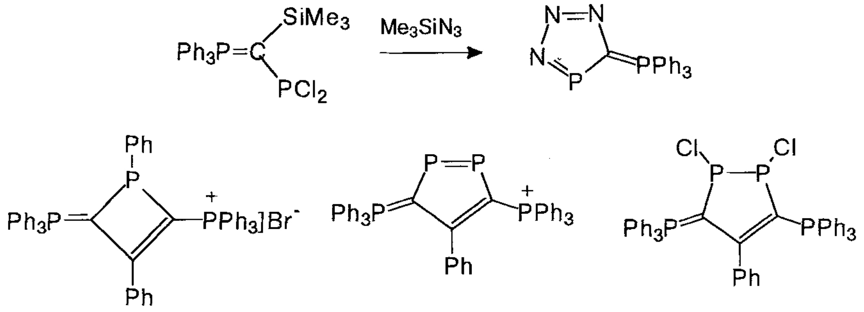
Schmidpeter and coworkers[239,240a,b] have synthesized the dichlorophosphino ylide **138**, an interesting initial compound for preparation of phosphorus ylides of unusual structure. When reacted with aluminum chloride it gives the ylidylphosphenium cation **139** and with bis(trimethylsilyl)phenylphosphine it gives 1,3-bis(triphenylphosphoniumylidyl)cyclotetraphosphine **140**. X-Ray crystallographic analysis of compound **140** revealed *trans* orientation of all the substituents of the four-membered ring (Scheme 4.19)[241]. Dichlorophosphinoylide **138** was also used by Schmidpeter and coworkers for the synthesis of the first stable phosphorus ylides with phosphorus sulfide and phosphorus disulfide groups on the ylide carbon atom[242-244a,b]. The chemistry of **141** and **142** was studied[244c].



a = $AlCl_3$; b = $PhP(SiMe_3)_2$; c = $(Me_3Si)_2S$ or $(Me_3Si)_2Se$; d= Na_2S_2 (Na_2Se)

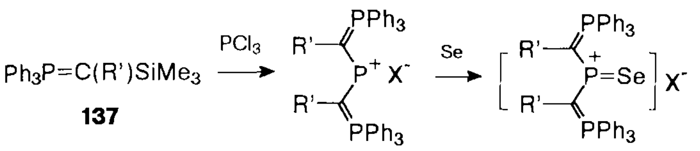
Scheme 4.19

Schmidpeter and coworkers[244e,f] synthesized four- and five-membered heterocycles with an exocyclic ylide group including heterocycles with a double P–P bond. Triphenylphosphonio-substituted triazophospholes and diazophospholes were prepared (Scheme 4.20)[244e]:



Scheme 4.20

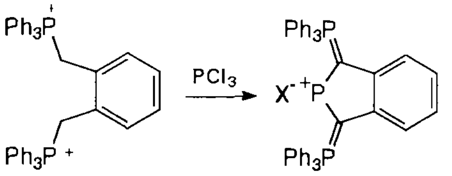
Bis(ylide)substituted phosphenium and phosphonium halides **143** are prepared by condensation of PCl_3 with trimethylsilyl ylides **137** (Eq. 4.72)[244d]. Compound **143** adds selenium to afford the bis-ylide-substituted selenoxophosphonium chloride **144**[244a,245]. Compound **143** was the first chalcogenphosphonium ion with a trigonal planar phosphorus atom isolated in the individual form[244,245].



137 **143** **144**

(4.72)

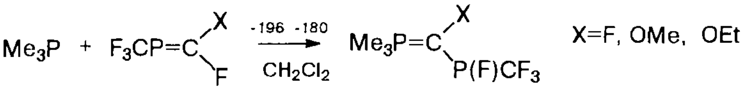
Diphosphoniumisophosphindole **145**, containing a two-coordinate phosphorus atom on the ylide carbon atom, has been synthesized by reaction of the corresponding bisphosphorane with phosphorus trichloride[243,245,246]. The crystal and molecular structure of the phosphorus ylide **145** have been described (Eq. 4.73)[245,249].



145

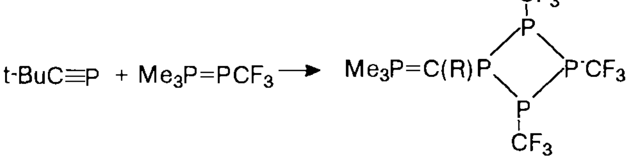
(4.73)

Grobe and coworkers[247a] have prepared phosphorus ylides substituted with the trivalent phosphorus atom on the ylide carbon atom by adding trimethylphosphine to fluorinated phosphaalkenes. The formation of the ylides was explained by the electrophilic character of the two-coordinate phosphorus atom (Eq. 4.74).



$$Me_3P + F_3CP{=}C(X)F \xrightarrow[CH_2Cl_2]{-196\ -180} Me_3P{=}C(X)P(F)CF_3 \qquad X{=}F,\ OMe,\ OEt \qquad (4.74)$$

Grobe[247b] has also performed a very interesting synthesis of a phophorus ylide **146** with a tetraphosphetene ring on the *a* carbon atom starting from the derivatives of mono- or two-coordinate phosphorus (Eq. 4.75):



146

(4.75)

The four-coordinate phosphorus atom efficiently stabilizes the ylide carbanion, which makes the transylidation reaction a general technique for the preparation of various C-phosphorus-substituted ylides containing phosphoryl or thiophosphoryl groups on the *a* carbon atom[117,209,250]. This method has also been used for the synthesis of ylides containing one, two, or three P=C groups on the four-coordinate phosphorus atom (Eq. 4.76)[154,238,251]:

$$2n\ \mathrm{Ph_3P{=}CHR} \xrightarrow{\mathrm{Ph_nP(S)Cl_{3-n}}} \mathrm{(Ph_3P{=}CR)_{3-n}P(S)Ph_n} \tag{4.76}$$

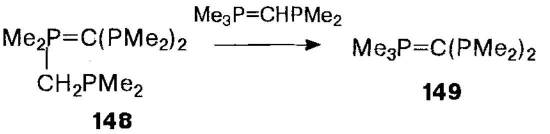
The salt method has also been used, although not so often, for the preparation of C-phosphorus-substituted ylides. Thus triphenylphosphonium diphenylphosphonomethylide can be obtained by the quaternization of triphenylphosphine with diphenyl chloromethylphosphonate on heating to 175°C (Eq. 4.77)[252]:

$$\mathrm{(PhO)_2PO)CH_2Cl} \xrightarrow{\mathrm{Ph_3P}} \mathrm{[(PhO)_2P(O)CH_2PPh_3]Cl^-} \xrightarrow[\mathrm{-HCl}]{\mathrm{B}} \mathrm{(PhO)_2P(O)CH{=}PPh_3} \tag{4.77}$$

The bis- and tris(diorganylphosphino)methanes are alkylated by alkyl halides with the formation of methylenephosphonium salts, which give carbodiphosphoranes[253] on dehydrohalogenation. Similarly, tris(diorganylphosphino)methanes give ylide bisphosphonium salts **147** (Eq. 4.78)[253–259]:

$$\mathrm{CH(PMe_2)_3} \xrightarrow{\mathrm{MeI}} \mathrm{[CH(\overset{+}{P}Me_3)_3]3I^-} \xrightarrow[\mathrm{-HI}]{} \underset{\textbf{147}}{\mathrm{[Me_3P{=}C(\overset{+}{P}Me_2)_3]2I^-}} \tag{4.78}$$

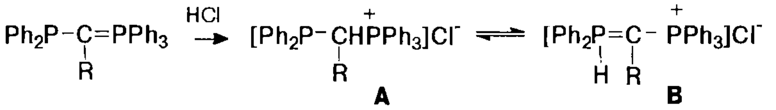
The ylide **148** (for the synthesis of the ylide **148** see Refs 255–264) readily undergoes recombination with trimethylphosphonium dimethylphosphino methylide to give the bisphosphino-substituted ylide **149** (Eq. 4.79)[74,151,254,255]:



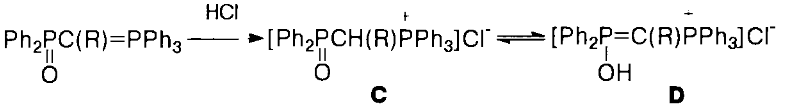
$$\underset{\textbf{148}}{\mathrm{Me_2\underset{\displaystyle CH_2PMe_2}{\underset{|}{P}}{=}C(PMe_2)_2}} \xrightarrow{\mathrm{Me_3P{=}CHPMe_2}} \underset{\textbf{149}}{\mathrm{Me_3P{=}C(PMe_2)_2}} \tag{4.79}$$

Phosphorus ylides stabilized with phosphorus, arsenic or antimony atoms are thermally stable. It has been confirmed by physicochemical studies[251,265] that tri- and pentavalent phosphorus atoms on the ylide carbon atom efficiently delocalize its electron density. Thus the effect of the phosphorus-containing groups X on the CH-acidity of the ylides $\mathrm{Ph_3P{=}CHX}$ decreases in the order: $\mathrm{P(O)(OR)_2 > P(O)Ph_2 > P(S)Ph_2 > PPh_2}$.

X-Ray crystallographic studies of element substituted phosphorus ylides reveal the shortening of the P=C bond in $\mathrm{Ph_3P{=}C(R)EPh_2}$ as (in Å): E = P 1.720[266], E = As 1.698[267] and E = Sb 1.692[268]. Two or three phosphonium groups on the ylide carbon atom further reduce the basicity of the compounds[268,270]. For instance, tris(triphenylphosphonium) methylide cannot be protonated even by strong acids. Bis(triphenylphosphonium)diphenylphosphinomethylide ($\mathrm{R = P^+Ph_3}$) is protonated on the trivalent phosphorus atom[215,216], whereas triphenylphosphonium diphenylphosphino(ethoxycarbonyl)methylide (R = CO_2Et) is protonated both on the *a* carbon atom and on the trivalent phosphorus atom[271]. Mastryukova et al.[272] have shown by NMR the existence of a tautomeric equilibrium between the **A** and **B** forms of compound (Eq. 4.79). The protonation of the triphenylphosphinoyl methylide leads to CH (**C**) or OH-protonated forms (**D**) depending on the properties of the substituents R. If R = CO_2Et the OH- and CH-protonated forms coexist in solution in a tautomeric equilibrium (Eq. 4.80)[273]:

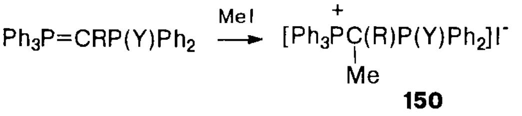


$$\mathrm{Ph_2P{-}\underset{R}{C}{=}PPh_3} \xrightarrow{\mathrm{HCl}} \underset{\mathbf{A}}{[\mathrm{Ph_2P{-}\underset{R}{\overset{+}{C}}HPPh_3}]\mathrm{Cl}^-} \rightleftharpoons \underset{\mathbf{B}}{[\mathrm{Ph_2\underset{H}{P}{=}\underset{R}{C}{-}\overset{+}{P}Ph_3}]\mathrm{Cl}^-} \qquad (4.80)$$

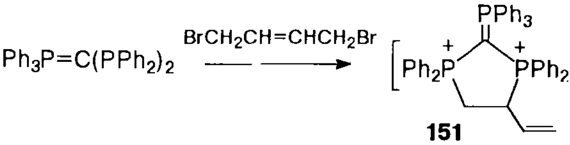


$$\mathrm{Ph_2\underset{O}{\underset{\|}{P}}C(R){=}PPh_3} \xrightarrow{\mathrm{HCl}} \underset{\mathbf{C}}{[\mathrm{Ph_2\underset{O}{\underset{\|}{P}}CH(R)\overset{+}{P}Ph_3}]\mathrm{Cl}^-} \rightleftharpoons \underset{\mathbf{D}}{[\mathrm{Ph_2\underset{OH}{\underset{|}{P}}{=}C(R)\overset{+}{P}Ph_3}]\mathrm{Cl}^-} \qquad (4.81)$$

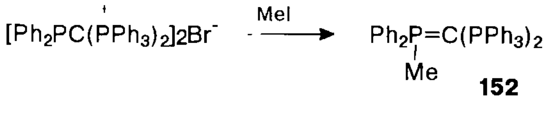
Alkylation of phosphine-phosphonium ylides occurs at the trivalent phosphorus atom with the formation of P-alkylated phosphonium salts **150** (Eq. 4.82), whereas the alkylation of phosphoryl- or thiophosphoryl-substituted phosphorus ylides produces the C-substituted phosphonium salts **151** (Eq. 4.83)[251,265,274]. The reaction of triphenylphosphonium bis(diphenylphosphino)methylide with 1,4-dibromobut-2-ene is a convenient method for the preparation of the ylide phosphonium salts **152** containing the 1,3-diphospholane ring (Eq. 4.84)[275,276]:



$$\mathrm{Ph_3P{=}CRP(Y)Ph_2} \xrightarrow{\mathrm{MeI}} \underset{\mathbf{150}}{[\mathrm{Ph_3P\underset{Me}{\underset{|}{\overset{+}{C}}}(R)P(Y)Ph_2}]\mathrm{I}^-} \qquad (4.82)$$

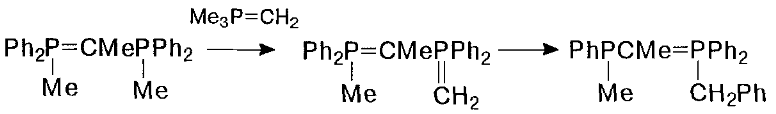


(4.83)



$$[\mathrm{Ph_2\overset{+}{P}C(PPh_3)_2}]2\mathrm{Br}^- \xrightarrow{\mathrm{MeI}} \underset{\mathbf{152}}{\mathrm{Ph_2\underset{Me}{\underset{|}{P}}{=}C(PPh_3)_2}} \qquad (4.84)$$

Some C-phosphorus-containing P-ylides undergo skeletal rearrangement. Under the action of trimethylphosphonium methylide, the phenyl group migrates from the phosphorus atom to the ylide carbon atom and the phosphonium salt **153** is convert'd into the phosphorus ylide **154** (Eq. 4.85)[277]:

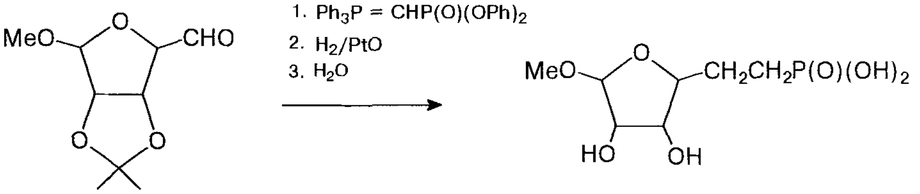


$$\underset{\text{Me}}{\text{Ph}_2\text{P}}\text{=CMe}\underset{\text{Me}}{\text{PPh}_2} \xrightarrow{\text{Me}_3\text{P=CH}_2} \underset{\text{Me}}{\text{Ph}_2\text{P}}\text{=CMe}\underset{\text{CH}_2}{\text{PPh}_2} \longrightarrow \underset{\text{Me}}{\text{PhP}}\text{CMe=}\underset{\text{CH}_2\text{Ph}}{\text{PPh}_2} \qquad (4.85)$$

153 **154**

Despite the relatively low nucleophilicity of ylides stabilized by the four-coordinate atom, they enter into the Wittig reaction with aldehydes on heating to form phosphorus-containing alkenes. The use of C-phosphorus-substituted ylides is used to prepare isosteric analogs of phosphates of natural origin[278–280].

Carbohydrates with protected hydroxy groups are easily alkenated by triphenylphosphonium diphenoxyphosphorylmethylide (Eq. 4.86). The vinylphosphonates formed as a result of the alkenation are hydrogenated over platinum or palladium oxide and hydrolyzed to form the phosphonic acids[281].

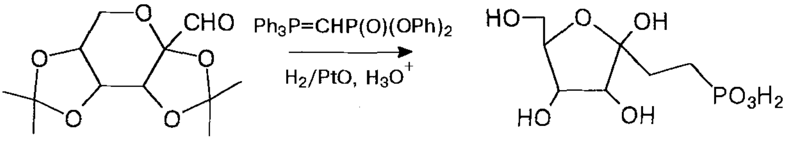


(4.86)

1,2-Dianhydro-1,2-dideoxy-3,4:5,6-di-O-isopropyliden-β-D-fructosoheptyl-pyranoso-1-diphenylphosphate (Eq. 4.86)

A solution of triphenylphosphonium diphenylphosphonatomethylide (1.5 g, 3.05 mmol) in DMSO was added to 2,3:4,5-di-*O*-isopropylidene-β-D-arabinosohexasilo-2,6-pyranose (0.71 g, 3.03 mmol) in absolute DMSO (15 mL) and the reaction mixture was mixed at room temperature for 48 h. The solvent was removed under vacuum, the residue was dissolved in chloroform (2 mL) and chromatographed through a silica gel column (20 g, 400 mL chloroform as eluent) to furnish a fraction containing the desired product together with triphenylphosphine oxide. After evaporation of the solvent the phenylphosphine oxide was precipitated with petroleum ether and removed by filtration. The pure desired product was obtained after solvent evaporation. Yield 0.71 g (48%).

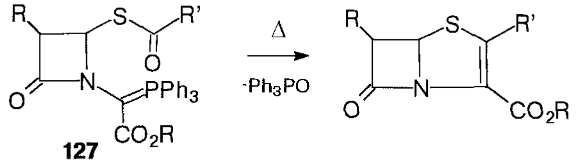
Using the same triphenylphosphonium diphenoxyphosphorylmethylide, the synthesis of the phosphonate analog of fructose-1-phosphate has been performed; this manifested the properties of a bioregulator of hexosephosphate transport systems (Eq. 4.87)[282]. Isosteric analogs of a series of phosphalipids and sugar phosphates have been prepared similarly[283–285].



(4.87)

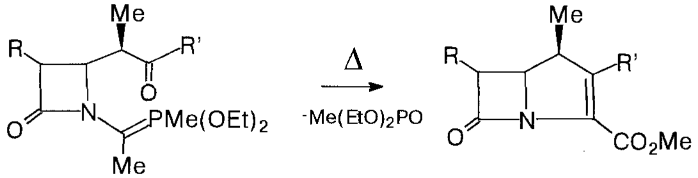
Huang et al.[286] synthesized phosphorus-containing pyrethroids using C-phosphorus-substituted ylides.

The phosphorus ylides **127** undergo an intramolecular Wittig reaction on heating and give penemates in high yields. These have found an important practical application in the synthesis of *β*-lactam antibiotics[287]. Syntheses of a series of other *β*-lactam antibiotics, derivatives of penemic and cefemic acids, have been described (Eq. 4.88)[287–295].



127

(4.88)

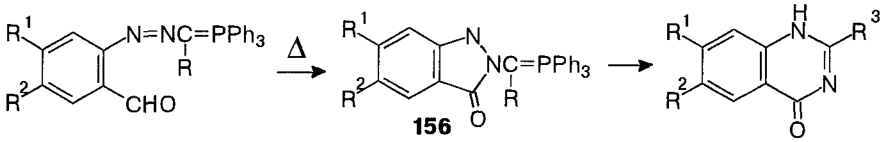


155

(4.89)

Japanese workers have prepared carbopenem derivatives in high yields by heating the phosphorus ylide **155** under reflux in xylene (Eq. 4.89). This technique has been proposed for industrial application[218,219].

The thermolysis of triphenylphosphonium azomethylide gives the ylides **156** that are converted into 4-oxo-1,4-dihydroquinazolines on further heating (Eq. 4.90)[227b,296]:

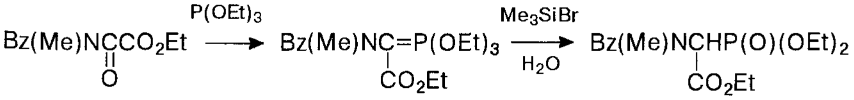


156

R=CO2Me, C(O)Me, SO2R, C(S)SMe

(4.90)

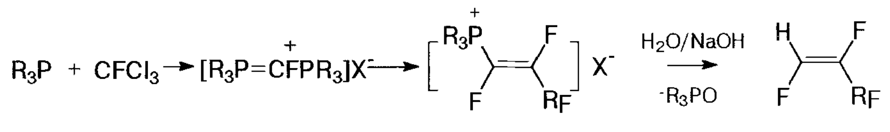
Japanese chemists have synthesized trialkoxyphosphonium ylides with a nitrogen atom on the ylide carbon atom and have converted them into the *α*-alkylaminophosphonates (Eq. 4.91) [297]:



$$\mathrm{Bz(Me)N\underset{\overset{\|}{O}}{C}CO_2Et \xrightarrow{P(OEt)_3} Bz(Me)N\underset{CO_2Et}{\overset{|}{C}}{=}P(OEt)_3 \xrightarrow[H_2O]{Me_3SiBr} Bz(Me)N\underset{CO_2Et}{\overset{|}{C}}HP(O)(OEt)_2}$$

(4.91)

Burton and coworkers[298] developed a method for the synthesis of the fluoroalkenes based on C-phosphorus-substituted ylides. The reaction presumably proceeds via a mechanism similar to that of the Wittig reaction and involves the formation of a betaine which decomposes to give phosphine oxide and vinylphosphonium salt **157**. The phosphonium salt **157** readily decomposes with cleavage of the C–P bond under the action of dilute alkali. The yields of fluoroalkenes do not exceed 45–62% (Eq. 4.92)[298,299].

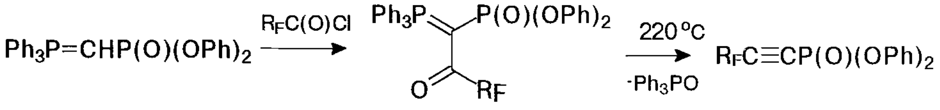


157 (4.92)

1,2;3,3;4,4;5,5-Nonafluoro-1-pentene (Eq. 4.92)[298]

Tri-*n*-butylphosphine (30.3 g, 37.4 mL, 0.15 mol) and diethyl ether (60 mL) were placed in a three-necked round-bottomed flask with stirring bar and a gas inlet tube. The solution was cooled with a water bath, trichlorofluoromethane (0.05 mol) was introduced into the flask, and the mixture was stirred for 1 h at 0°C, then for 3 h at room temperature. The phosphonium salt was obtained in 95% yield. Butanoyl fluoride (0.08 mol) was added to the phosphonium salt and rapid reaction resulted in *cis*-tributyl-1,2;3,3;4,4;5,5-nonafluoro-1-pentenphosphonium chloride in 85% yield. Hydrolysis of the phosphonium chloride was performed by addition of sodium hydroxide (50%, 6 mL). The reaction mixture was flash-distilled, dried with magnesium sulfate, and purified by fractional distillation. Yield 6.0 g (52%). The purity is 95%.

Perfluoroalk-1-yn-vinylphosphonates are obtained by pyrolysis of 2-hydroxyalkenyltriphenyl-phosphonium ylides, which follows an intramolecular Wittig-type reaction (Eq. 4.93)[300]:



(4.93)

General method for the synthesis of 1-perfluoroalkylphosphonates (Eq. 4.93)[300]

Excess perfluoroacetylfluoride (2.2 mmol) was introduced into a solution of triphenylphosphonium diphenoxyphosphorylmethylide (1.1 mmol) in absolute benzene (10 mL) at 50°C and the reaction mixture was stirred at this temperature for 1 h. The precipitate of the phosphonium salt was removed by filtration and the solvent was evaporated. The residue was purified by column chromatography on silica gel (with 1:1 Dichloromethane–petroleum ether as eluent). The triphenylphosphonium perfluoroacyldiphenoxyphosphoryl methylide was obtained in almost 100% yield and pyrolyzed in vacuo (8 mm) at 220°C. The pyrolysate was collected in a trap at –75°C. After distillation or crystallization the pure perfluoroalkynylphosphonate was obtained.

C-phosphine-substituted phosphorus ylides are used as ligands in transition metal complexes[226,260–264]. Thus substitution of ligands in chromium carbonyl complexes $Cr(CO)_5L$, where L = THF, C_7H_8, $Me_2S(O)CH_2$ by C-phosphine-substituted phosphorus ylides leads to cyclic and acyclic phosphorus ylides with a metal–phosphorus(III) bond[184,301].

Carbodiphosphorane dicarbanions stabilized by two phosphonium groups provide an example of C-phosphorus-substituted ylides important for synthesis (Chapter 3)[302,325].

4.4.2 Phosphorus Ylides Containing Group VIA Elements

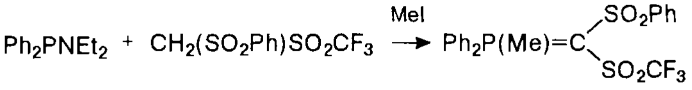
The phosphorus ylides stabilized by oxygen, sulfur, selenium, or tellurium atoms are very different in their structures and properties. The chemistry of these ylides is being rapidly developed. Convenient procedures for their preparation have been elaborated and their chemical properties have been studied. Ylides stabilized by Group VIA elements are used in the synthesis of natural substances and biologically active compounds.

The very stable C-sulfonyl-substituted ylides are the most readily available phosphorus ylides of this group. They can be prepares by simple methods, such as the direct phosphorylation of sulfonylalkanes by polyhalophosphoranes in the presence of triethylamine (Eq. 4.95)[326], (Eq. 4.96)[327] the salt method in the presence of organic bases (Eq.4.96),[327,328] or by reaction of diphenyldialkylaminophosphines with bis(sulfonyl)methanes and alkyl halides (Eq. 4.97)[329]: Heating of phenyliodonium ylides with triphenylphosphine in benzene in the presence of copper acetylacetonate as a catalyst gives phosphonium ylides in high yield (Eq. 4.98.)[330,331].

$$Ph_3PCl_2 + CH_2(SO_2R)_2 \xrightarrow[-Et_3N\cdot HCl]{Et_3N} Ph_3P{=}C(SO_2R)_2 \qquad (4.94)$$

$$Ph_3PCl_2 + CH_3SO_2CF_3 \xrightarrow[-Et_3N\cdot HCl]{Et_3N} Ph_3P{=}CHSO_2CF_3 \qquad (4.95)$$

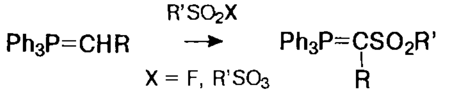
$$Ph_3P + RSO_2CH_2Br \longrightarrow [Ph_3\overset{+}{P}CH_2SO_2R]Br^- \longrightarrow Ph_3P{=}CHSO_2R \qquad (4.96)$$



$$Ph_2PNEt_2 + CH_2(SO_2Ph)SO_2CF_3 \xrightarrow{MeI} Ph_2P(Me){=}C\begin{matrix}SO_2Ph\\SO_2CF_3\end{matrix} \qquad (4.97)$$

$$PhI{=}C(SO_2R)_2 + Ph_3P \longrightarrow Ph_3P{=}C(SO_2R)_2 + PhI \quad R{=}Me, Ph \qquad (4.98)$$

The sulfonyl ylides **158** can be obtained by transylidation of phosphorus ylides with sulfonyl fluorides or sulfonic anhydrides (Eq. 4.99, Table 4.2)[149,328] and reaction of phosphorus ylides with arenesulfonyl chlorides results in chloro-substituted phosphorus ylides **158** rather than sulfonyl-substituted ylides (Eq. 4.100)[328]:



$$Ph_3P{=}CHR \xrightarrow[X\,=\,F,\ R'SO_3]{R'SO_2X} Ph_3P{=}\underset{\displaystyle R}{\underset{|}{C}}SO_2R' \qquad (4.99)$$

158

$$\mathrm{Ph_3P{=}CH_2} \xrightarrow{\mathrm{RSO_2Cl}} \mathrm{[Ph_3\overset{+}{P}CH_2Cl]RSO_2^-} \xrightarrow[\mathrm{-[Ph_3\overset{+}{P}Me]RSO_2^-}]{\mathrm{Ph_3P{=}CH_2}} \mathrm{Ph_3P{=}CHCl} \qquad (4.100)$$

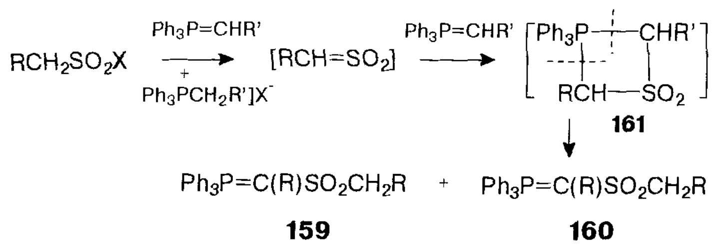
Reaction of phosphorus ylides with alkenesulfonyl halides is followed by rearrangement, which results in migration of substituent R^1 from the ylide carbon atom to the carbon atom of the SO_2CH_2 group and migration of substituent R^2 to the ylide carbon atom. A mixture the isomers of C-sulfonyl-substituted phosphorus ylides **159** and **160** is thus formed; the ratio depends on the nature of the substituents R^1 and R^2 (Eq. 4.101)[328,331]:

$$\mathrm{R'CH_2SO_2Cl} \xrightarrow{\mathrm{Ph_3P{=}CHR}} \underset{\mathbf{159}}{\mathrm{Ph_3P{=}C(R)SO_2CH_2R'}} + \underset{\mathbf{160}}{\mathrm{Ph_3P{=}C(R')SO_2CH_2R}} \qquad (4.101)$$

Table 4.2. Triphenylphosphonium alkyl- and arylsulfonylalkylides **158** (Eq. 4.99)

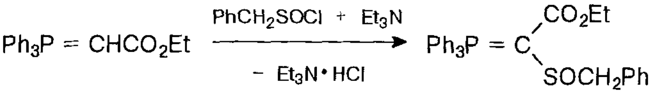
R	R'	Yield (%)	mp	Ref
H	Me	70	202-204°C	331
H	Et	83	200-201	331
H	i-Bu	63	125-126	331
H	$PhCH_2$	63	172-173	331
H	Ph	78	144-147	328
H	$4\text{-}MeOC_6H_4$	67	172-174	328
H	$4\text{-}ClC_6H_4$	74	183-185	328
Me	$t\text{-}BuCH_2$	50	120	331
Me	Bz	30	172.5	331
t-Bu	Me	69	146-147	331
t-Bu	Et	76	120	331
Ph	Me	95	172-174	331
Ph	Et	94	172.5	331
Ph	$t\text{-}BuCH_2$	77	163.5-164.5	331
Ph	Bz	91	210-211	331

The reaction presumably proceeds via the formation of sulfenes $R^2CH{=}SO_2$, which give an unstable four-membered cyclic intermediate **161** as a result of the addition to phosphorane, and are subsequently converted into the isomers **159** and **160** (Scheme 4.21):



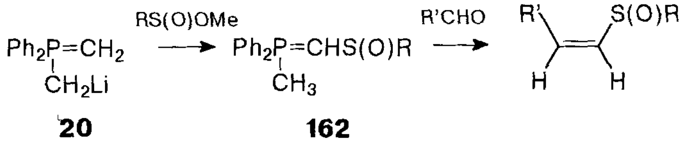
Scheme 4.21

The reaction of stabilized ylides with sulfinyl chlorides in the presence of triethylamine is used to introduce the sulfinyl group to the phosphorus atom. This reaction presumably proceeds via the intermediate formation of sulfines (Eq. 4.102)[332–334]:



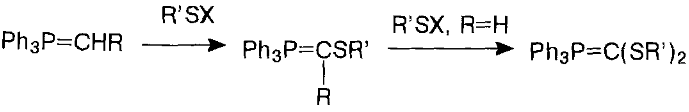
(4.102)

The reaction of diylides **20** (R = H) with sulfinates leads to the formation of C-sulfinylylides **162**, which undergo the Wittig reaction with aldehydes with excellent stereoselectivity (*E*/*Z* > 91/9). The same reaction with a chiral sulfinate leads to chiral *E*-vinylsulfoxides (*E*/*Z* > 99/1), with more than 96% inversion of configuration at the sulfur atom (Eq. 4.103)[50]:



(4.103)

There are convenient procedures for the preparation of the phosphorus ylides containing a bivalent sulfur atom on the *a* carbon atom. The reactions of stabilized and unstabilized phosphorus ylides with sulfenyl chlorides in benzene or THF at 20°C and a reagent ratio of 2:1 or 3:1 are most often used. As a result of the transylidation reaction, ylides containing one or two thio groups on *α* carbon atom are formed[334–338]. Tolylthio *p*-toluenesulfonate, *N*-methyl-*N*-phenylthioacetamide[162], and dimethylsuccinimidosulfonium chloride[345,355,359] are used as thioarylating reagents (Eq. 4.104):



$$\mathrm{Ph_3P{=}CHR} \xrightarrow{\mathrm{R'SX}} \mathrm{Ph_3P{=}\underset{\displaystyle R}{\underset{|}{C}}SR'} \xrightarrow{\mathrm{R'SX,\ R{=}H}} \mathrm{Ph_3P{=}C(SR')_2} \tag{4.104}$$

X= Cl, ArSO$_2$, N(Me)COMe; R= H, Ar

The reaction of phosphorus ylides with disulfides in benzene gives the ylides **163** in a yield of approximately 90% (Eq. 4.105)[334,335,340]:

$$\mathrm{Ph_3P{=}CHC(O)R} \xrightarrow{\mathrm{R'SSR'}} [\mathrm{Ph_3\overset{+}{P}CH(SR')C(O)R}]\ \mathrm{RS^-} \longrightarrow \underset{\textbf{163}}{\mathrm{Ph_3P{=}C(SR')C(O)R}} \qquad (4.105)$$

R=Me, MeO; R=R$_2$NC(S), EtO$_2$C

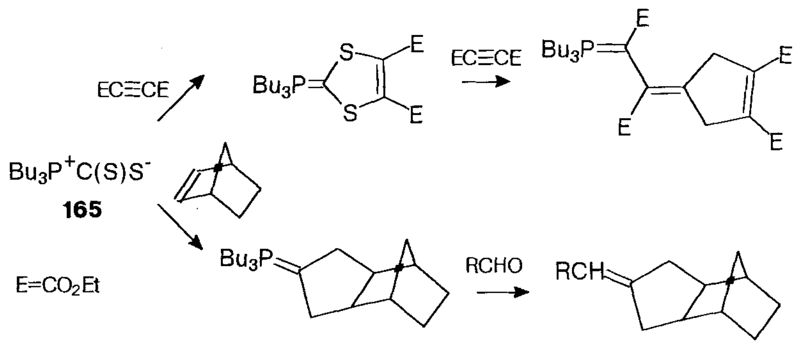
The synthesis of ylides **164** with two thioether groups on the carbon atom by reaction of tertiary phosphines with bisalkyl(aryl)thiocarbenes has been reported[341,342]. Dithiocarbenes were generated by the action of sodium hydride on the corresponding tosylhydrazone[361] or by the decomposition of tris(phenylthio)methyllithium (Eq. 4.106)[342]:

$$\mathrm{R_3P} \xrightarrow{[\mathrm{(R'S)_2C:}]} \underset{\textbf{164}}{\mathrm{R_3P{=}C(SR')_2}} \qquad \mathrm{R{=}\ Bu,Ph,\ R'{=}Et,Ph,} \qquad (4.106)$$

The most important method of synthesis of ylides containing alkylthio groups on the *a* carbon atom is the dehydrohalogenation of phosphonium salts by means of organolithium derivatives. Ylides synthesized by this method have been used in the Wittig reaction without isolation from the reaction solutions (Eq. 4.107)[8,9]:

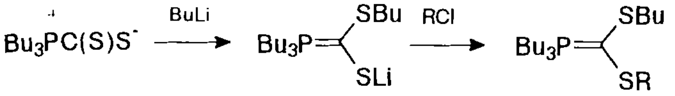
$$[\mathrm{Ph_3\overset{+}{P}CH_2SR}]\mathrm{Cl^-} \xrightarrow{\mathrm{PhLi}} [\mathrm{Ph_3P{=}CHSR}] \xrightarrow{\mathrm{R'CHO}} \mathrm{RSCH{=}CHR'} \qquad (4.107)$$

The adduct of tributylphosphine with carbon disulfide, **165**, which was isolated more than a hundred years ago by Hoffmann[343], has recently been studied intensely. The ability of the adduct to enter into cycloaddition reactions with the formation of phosphorus ylides containing the dithiolane ring is not the least reason for such interest (Scheme 4.22)[344,345]:



Scheme 4.22

Polezhayeva and coworkers have introduced the adduct **165** into reactions with various dipolarophiles to prepare C-dithio-substituted phosphorus ylides of both cyclic and acyclic structure (Eq. 4.108)[346]:



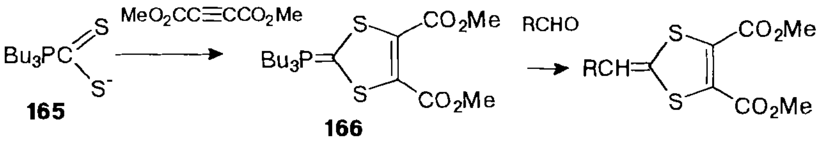
(4.108)

165

R=Me3Si, PhCH2, Ph2P

The ability of dithia- and tetrathiafulvenes to generate the electroconducting salts has stimulated great interest in phosphorus ylides containing thiafulvene groups[347 351,508]. Thus 2-thioxo- and 2-oxo-1,3-dithiol-4-ylmethylides have been proposed as reagents for the synthesis of 1,3-dithia- and tetrathiafulvenes[352].

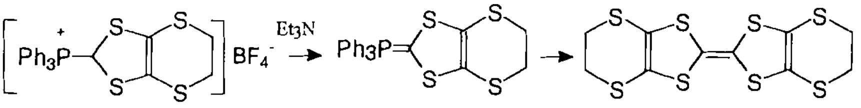
The addition of dimethyl acetylenedicarboxylate to adduct **165** has led to the highly reactive cyclic ylide **166**, which enters into the Wittig reaction and yields dithiafulvenes with π-donating properties (Eq. 4.109)[350]:



165 **166**

(4.109)

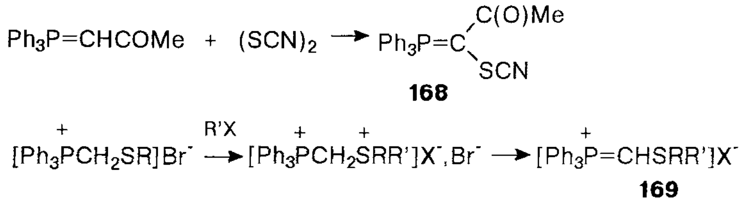
1,3-Dithiol-2-ylides have been generated from the corresponding phosphonium salts with the dithiolane ring even under the action of triethylamine or diisopropylamine[347]. Ylides **167** containing the 1,3-dithiol-2-ylide fragment have been used for the preparation of the corresponding polyformyltetrathiafulvalenes with a strong π-donating capacity (Eq. 4.110)[349]:



167

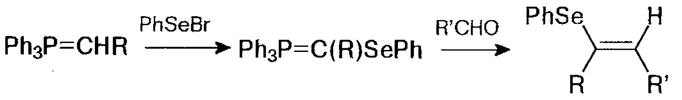
(4.110)

More detailed information about the synthesis of tetrathiofulvenes by Wittig olefination can be found in Chapter 6 of this book. Triphenylphosphonium 2-oxo-1-thiocyanopropylide, **168**, has been synthesized in 65% yield by reaction of triphenylphosphonium 2-oxopropylide with thiocyanogen[339]. Alkylation of the alkylthiomethyl-triphenylphosphonium salt gives the phosphonium sulfonium salt, which yields the ylide-sulfonium salt **169** upon dehydrohalogenation (Scheme 4.23)[353]:



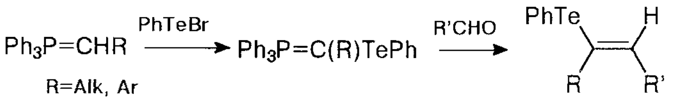
Scheme 4.23

The reaction of phosphorus ylides with phenylselenyl bromide has been proposed for the preparation of C-selenium-substituted ylides[354]. The C-selenium substituted phosphorus ylides enter into the Wittig reaction with aldehydes to yield phenylselenoalkenes in high yield (Eq. 4.111)[354–358]:



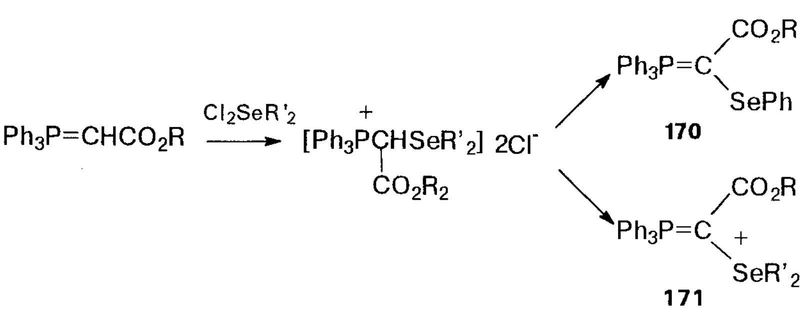
(4.111)

C-Tellurium-substituted phosphorus ylides have been synthesized similarly and used for the preparation of tellurium-substituted alkenes (Eq. 4.112)[359]:



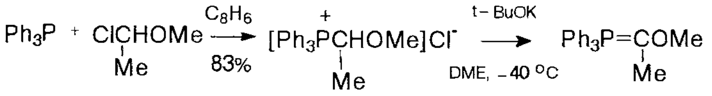
(4.112)

The reaction of dichloroselenides with triphenylphosphonium alkoxycarbonylmethylides results in the C-selenium-substituted ylides **170** or phosphonium selenonium ylides **171**. If the intermediate salts **171** contain two alkyl groups, they are dehydrochlorinated by excess phosphorus ylide with the formation of ylide-selenonium salts **171**. If there are phenyl and alkyl groups at the selenium atom, the ylide **170** is formed (Scheme 4.24)[360,361].



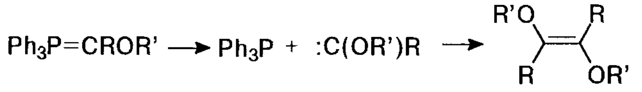
Scheme 4.24

Phosphorus ylides with alkoxy and aroxy groups on the α carbon atom are usually obtained by the salt method[363,364]. Thus treatment of a suspension of a finely ground phosphonium salt with phenyllithium in ether gives a bright-red solution of *C*-alkoxymethylide, which readily reacts with aldehydes and ketones to give alkyl vinyl ethers[345,363]. Triphenylphosphonium α–methoxyethylide is prepared by reaction of triphenylphosphine with α–chloroethylmethyl ether in benzene. The phosphonium salt is then treated with potassium *tert*-butoxide in dimethoxyethane at –40°C for a few minutes (Eq. 4.113). The red solution of the highly active ylide is formed and this readily alkenates aldehydes and ketones[365].



$$Ph_3P + \underset{Me}{ClCHOMe} \xrightarrow[83\%]{C_6H_6} [Ph_3P\overset{+}{}\underset{Me}{CHOMe}]Cl^- \xrightarrow[DME,\ -40\ ^{\circ}C]{t-BuOK} Ph_3P{=}\underset{Me}{COMe} \qquad (4.113)$$

Ylides with oxygen or bivalent sulfur atoms on the α carbon atom are unstable. They are normally used for further one-pot chemical transformation. *Ab initio* calculations show that although the presence of the oxygen atom on the negatively charged carbon atom should generally stabilize the carbanion, this does not happen for phosphorus ylides. C-Oxygen-substituted phosphorus ylides have an enhanced tendency to dissociate into carbenes and tertiary phosphine, so they can be regarded as the carbene complexes of tertiary phosphines. The formation of carbenes at the intermediate stage of the reaction is confirmed by ab initio calculations by the extended Huckel method in the 6-31 basis set (Eq. 4.114)[16].



(4.114)

Ylides **172** also decompose readily with the formation of carbenes, which give 1,2-diketones as a result of intramolecular rearrangement (Eq. 4.115)[366]:

$$\underset{\mathbf{172}}{Ph_3P{=}C(R)OCOC(O)R'} \xrightarrow[-30^{\circ}]{} Ph_3P + :C(R)OC(O)R' \longrightarrow RC(O)C(O)R' \qquad (4.115)$$

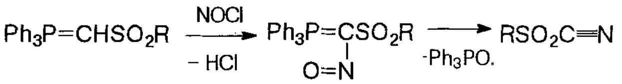
C-Sulfonyl-substituted ylides are characterized by high thermal stability as a result of efficient delocalization of the negative charge on the ylide carbon atom by the hexavalent sulfur atom; this has been confirmed by physicochemical studies[367–372], in particular by X-ray crystallography[348,393]. The IR spectra of ylides containing sulfonyl or sulfinyl groups on the carbon atom show a considerable shift of the S=O and SO_2 frequencies towards the long-wave region owing to the efficient delocalization of the carbanion negative charge by these groups[329,367–370]. Triad prototropic tautomerism is typical of bis(arylsulfonyl) methylphosphine oxides, which exist in the CH-phosphine oxide form in crystals and as tautomeric mixtures of the OH-ylide and CH-phosphine oxide forms in solution; these forms can be easily detected by spectroscopy (Eq. 4.116)[371,372]:

$$\mathrm{Ph_2P(=O)CH(SO_2Ar)_2} \rightleftharpoons \mathrm{Ph_2P(OH)=C(SO_2Ar)_2} \qquad (4.116)$$

Hydrogen on the *a* carbon atom of C-sulfonyl-substituted ylides is active and can be readily substituted by various groups. The treatment of the ylides with butyllithium results in substitution of the hydrogen atom by lithium with the formation of the dicarbanion **173**, which reacts with chlorine-containing electrophiles (Eq. 4.117)[328]:

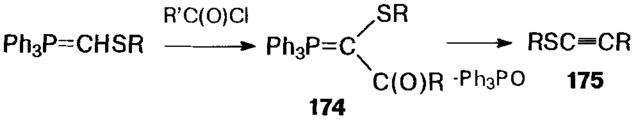
$$\mathrm{Ph_3P{=}CHSO_2R} \xrightarrow{\mathrm{BuLi,\,-10^{\circ}}} \underset{\mathbf{173}}{[\mathrm{Ph_3\overset{+}{P}\overset{-}{C}Ts}]\mathrm{Li^+}} \xrightarrow{\mathrm{EtOCOCl}} \mathrm{Ph_3P{=}C(Ts)CO_2Et} \qquad (4.117)$$

The reaction of C-sulfonyl-substituted ylides with nitrosyl chloride in pyridine leads to substitution of the hydrogen atom on the *a* carbon atom by a nitroso group. The ylide thus formed is converted into a sulfonyl cyanide in a Wittig-type intramolecular reaction (Eq. 4.118)[328,374]:

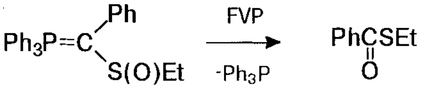


$$\mathrm{Ph_3P{=}CHSO_2R} \xrightarrow[\mathrm{-\,HCl}]{\mathrm{NOCl}} \mathrm{Ph_3P{=}C(N{=}O)SO_2R} \xrightarrow[\mathrm{-Ph_3PO.}]{} \mathrm{RSO_2C{\equiv}N} \qquad (4.118)$$

Flash-vacuum pyrolysis of the acylmethylides **174** obtained by the reaction of C-alkylthio-substituted ylides with acid chlorides produces the alkyl(aryl) thioacetylenes **175** in good yields (Eq. 4.119)[328,338,374–377]. Flash-vacuum pyrolysis of sulfinyl-stabilized ylides gives thioesters in satisfactory yield (Eq. 4.120)[377]:

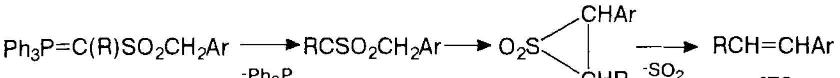


174 **175** (4.119)

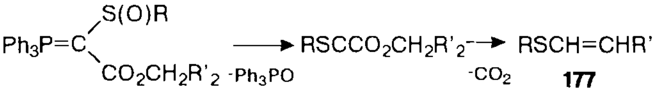


(4.120)

Flash-vacuum pyrolysis of sulfonyl- and sulfinyl-stabilized phosphorus ylides is accompanied by elimination of phosphine or phosphine oxide with the formation of thio-, sulfinyl-, or sulfonylcarbenes, which give the alkenes **176** and **177** as a result of rearrangements and insertion reactions (Eq. 4.121,122)[376,377]:


176

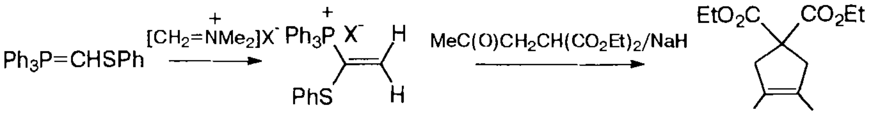
(4.121)


177

$$Ph_3P{=}C\begin{matrix}S(O)R\\CO_2CH_2R'_2\end{matrix} \xrightarrow[-Ph_3PO]{} RSCCO_2CH_2R'_2 \xrightarrow[-CO_2]{} RSCH{=}CHR'$$

(4.122)

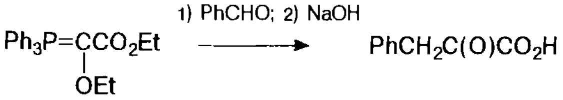
The substituted vinylphosphonium salts **178** are obtained by reaction of phenylthiomethylides with iminium salts; they are used in the synthesis of cyclopentadienes (Eq. 4.123)[378]:


178

(4.123)

C-Sulfonyl-substituted ylides are characterized by weak basicity and nucleophilicity, which accounts for their low activity in the Wittig reaction. The monosubstituted ylides react only with aldehydes, and not with ketones. Triphenylphosphonium bis-sulfonylmethylides also do not react with carbonyl compounds. In contrast, phosphorus ylides with alkylthio, alkoxy, or aryloxy groups on the α carbon atom readily enter into the Wittig reaction with various carbonyl compounds[379 390].

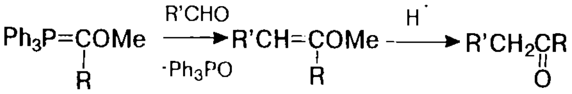
The reaction of ethoxy(ethoxycarbonyl)methylides with aldehydes and the subsequent hydrolysis of the vinyl ethers formed is a convenient means of preparation of oxocarboxylic acids (Eq. 4.124)[383]:



$$Ph_3P{=}\underset{OEt}{C}CO_2Et \xrightarrow{1)\ PhCHO;\ 2)\ NaOH} PhCH_2C(O)CO_2H$$

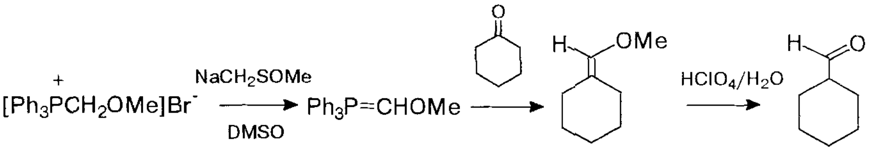
(4.124)

Ylides with alkoxy groups at the ylide carbon atom alkenate both aldehydes and ketones with the formation of the vinyl ethers **179**. On hydrolysis these give the corresponding aldehydes (R^1 = H) or ketones (R^1 = Me); the latter can again be introduced into the Wittig reaction with triphenylphosphonium methoxymethylide, thereby extending the carbon chain (Eq. 4.125,126)[379-381]:


179

$$Ph_3P{=}\underset{R}{C}OMe \xrightarrow[-Ph_3PO]{R'CHO} R'CH{=}\underset{R}{C}OMe \xrightarrow{H^+} R'CH_2\underset{O}{C}R$$

(4.125)

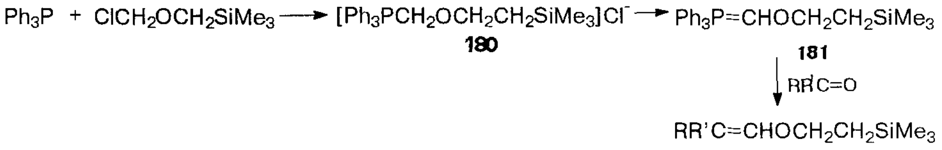


(4.126)

Triphenylphosphonium methoxymethylide (Eq. 4.126)[391]

A solution of methoxymethyltriphenylphosphonium chloride (3.5 g, 10 mmol) in absolute DMSO (15 mL) was added dropwise with stirring to a solution of dimsyl sodium (prepared from sodium hydride (10 mmol) and DMSO (10 mL). The reaction mixture was stirred at 55°C for 30 min and then cooled to room temperature. Cyclohexanone (1.8 mmol) was added and the reaction mixture was stirred for 10 h at 70°C. The mixture was then cooled, diluted with water (150 mL), and extracted with ethyl acetate (3 x 50 mL). The extracts were dried with sodium sulfate and the solvent was removed under vacuum. The residue was dissolved in ether (30 mL) and $HClO_4$ (70%, 7–8 mL) was added. The mixture was stirred at room temperature for 10–12 h, diluted with ice water, and extracted with diethyl ether (3 x 50 mL). The extracts were dried with sodium sulfate and the solvent was evaporated. The cyclohexanecarboxaldehyde was purified by column chromatography.

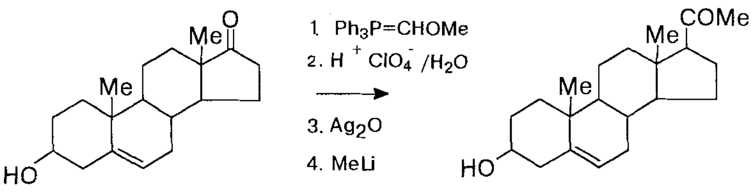
The silicon-containing α alkoxymethylides **180** are especially convenient for this purpose. The vinyl ethers **181** that are formed by reaction of ylide **180** with aldehydes and ketones give aldehydes on treatment with 5% hydrogen fluoride in acetonitrile or with perchloric acid (Scheme 4.25)[382]:



$$\begin{tikzcd}[column sep=small] Ph_3P + ClCH_2OCH_2SiMe_3 \arrow[r] & \underset{\mathbf{180}}{[Ph_3PCH_2OCH_2CH_2SiMe_3]Cl^-} \arrow[r] & \underset{\mathbf{181}}{Ph_3P{=}CHOCH_2CH_2SiMe_3} \arrow[d, "RR'C{=}O"] \\ & & RR'C{=}CHOCH_2CH_2SiMe_3 \end{tikzcd}$$

Scheme 4.25

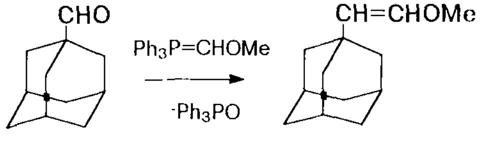
This method has been used for the preparation of various steroid aldehydes[381-390]. Danishefski and coworkers[391,392] have developed a simple method for the preparation of pregnenolone **183** by reaction of androstenolone **182** with the C-oxygen-substituted ylide prepared by dehydrohalogenation of the methoxymethyltriphenylphosphonium salt with sodium hydride in DMSO (Eq. 4.127):



182 **183**

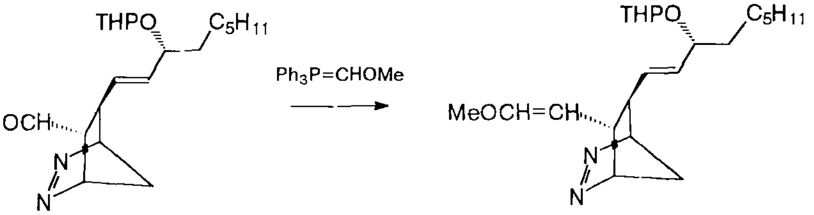
(4.127)

Triphenylphosphonium methoxymethylide enters into the Wittig reaction with sterically hindered carbonyl compounds. For instance, it readily alkenates adamantane-1-carboxaldehyde in ether at –40°C (Eq. 4.128)[393]:



(4.128)

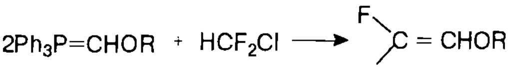
Corey et al.[395] have shown that dehydrochlorination of α-methoxyalkylphosphonium salts proceeds smoothly under the action of lithium diisopropylamide. The ylides thus obtained have been used to synthesize the 9,11-aza analogs of prostaglandin endoperoxide PGH_2 **184** (Eq. 4.129):



184

(4.129)

The Wittig-type reactions of triphenylphosphonium alkoxymethylides with chlorodifluoromethane are a synthetic route to *gem*-difluoroolefins **185** (Eq. 4.130)[394]:



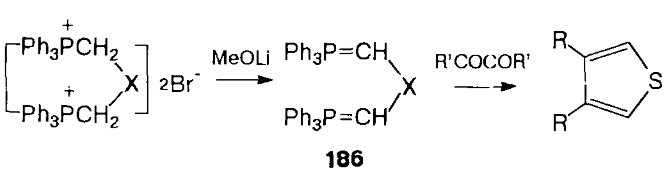
$$2Ph_3P{=}CHOR + HCF_2Cl \longrightarrow F_2C{=}CHOR$$

R=Me, i-Bu

185

(4.130)

Bis(triphenylphosphoniomethyl)oxide and -sulfide are converted into bis-ylides **186** by lithium methoxide. The bis-ylides **186** are introduced into the Wittig reaction with dialdehydes or diketones for the synthesis of various heterocycles including macrocycles[396]. For instance, reaction of ylides **186** with β-diketones gives furan and thiophene derivatives (Eq. 4.131), and reaction with cycloheptatriene-1,6-dicarbaldehyde and biphenyl-2,2′-dialdehyde gives 4,9-methanooxa[22]-annulenes[397] (Chapter 6).



186

(4.131)

4.4.3 C-Halogen-Substituted Phosphorus Ylides

Interest in C-halogen-substituted phosphorus ylides has arisen because of their possible application for the preparation of haloalkenes, which are valuable synthetic reagents[5,13,399–401]. C-Halogenated ylides can be obtained by dehydrohalogenation of phosphonium salts or by reaction of a tertiary phosphine with a source of the mono- or dihalomethylene fragment. The addition of a halocarbene or carbenoid to a tertiary phosphine is one of the most important methods of synthesis of phosphorus ylides bearing one or two halogen atoms on the α carbon atom (Eq. 4.132):

$$R_3P + XX'CYZ \xrightarrow[-XX']{} R_3P{=}CYZ \longleftarrow R_3P + :CYZ \qquad (4.132)$$

The oldest method for the synthesis of C-halogen-containing ylides is treatment of polyhalomethanes with strong bases in the presence of a tertiary phosphine[401–407]. In this way, in 1961, Seyferth et al.[405] and Wittig and Schlosser[406] obtained triphenylphosphonium chloromethylide **187** in 65% yield from dichloromethane, butyllithium, and triphenylphosphine (Eq. 4.133).

$$Ph_3P + CH_2Cl_2 \xrightarrow{BuLi} \underset{\mathbf{187}}{Ph_3P{=}CHCl} \qquad (4.133)$$

$$Ph_3P + CH_2Cl_2 \xrightarrow{t\text{-}BuOK} Ph_3P{=}CXCl \xrightarrow{RCHO} RCH{=}CXCl \qquad (4.134)$$

188 (x=Cl), **189** (X=F)

Dichlorocarbene generated from chloroform by the action of potassium *tert*-butoxide reacts with triphenylphosphine to give a suspension of triphenylphosphonium dichloromethylide **188** which is used in the Wittig reaction without isolation from the reaction mixture (Eq. 4.134). The ylide $Ph_3P{=}CFCl$ **189** containing chlorine and fluorine on the α carbon atom has been prepared by Speciale and Ratts in the same way[402]. The ylide is formed by capture of chlorofluorocarbene by triphenylphosphine (Eq. 4.134).

Triphenylphosphonium chloromethylide solution (Eq. 4.133)[405,406]

A solution of butyllithium (40 mmol) in diethyl ether (22 mL) was added dropwise to a solution of triphenylphosphine (35 mmol) in dichloromethane (45 mL) at -60°C. The solution of ylide is ready for chemical synthesis.

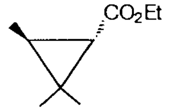
Triphenylphosphonium dichloromethylide (Eq. 4.134)[402]

A solution of potassium tert-butoxide (0.5 mol) in excess *tert*-butanol was placed in a three-necked round-bottomed flask and excess *tert*-butanol was removed under vacuum. The potassium *tert*-butoxide residue was cooled to 0–5°C, mixed with triphenylphosphine (0.5 mol), and then the solution of chloroform (0.5 mol) in heptane was added with vigorous stirring. *p*-Nitrobenzaldehyde was added to a suspension of the prepared ylide in heptane at 0–10°C with vigorous stirring The course of the reaction was monitored by TLC. The precipitate of triphenylphosphine oxide was removed by filtration, the filtrate was evaporated under vacuum, and the residue was recrystallized from methanol. For separation of the triphenylphosphine a solution of mercury chloride in absolute ethanol was added to the product. The insoluble complex of mercury chloride and triphenylphosphine was separated, the solvent was evaporated and the residue was recrystallized.

Triphenylphosphonium dichloromethylide **188** has been also synthesized in heterogeneous media, dichlorocarbene being generated from chloroform under the action of 50% alkali in the presence of a phase-transfer catalyst (TEBA) and triphenylphosphine. In this case ylide in the nascent state enters the Wittig reaction[408]. When a solution in benzene of chloroform (or dichloromethyl thioether), triphenylphosphine, benzaldehyde and a catalytic amount of TEBA was vigorously stirred at room temperature for 1.5 h with 40% aqueous sodium hydroxide, *β*-chlorostyrene derivatives **190** were prepared in yields of approximately 40–50%. This reaction has been used for the preparation of pyrethroids '(Eq. 4.135)[409,410]:

$$Ph_3P + RCHCl_2 \xrightarrow{NaOH/H_2O} Ph_3P{=}C(Cl)R \xrightarrow[-Ph_3PO]{PhCHO} \underset{\mathbf{190}}{PhCH{=}C(Cl)R} \qquad (4.135)$$

R=Cl, RS ,



β,β-Dichlorostyrene (Eq. 4.135)[408]

An aqueous solution of sodium hydroxide (40%, 20 mL) was added dropwise with vigorous stirring to a solution of chloroform (60 mL), benzaldehyde (5.3 g, 0.05 mmol), triphenylphosphine (13.1 g, 0.005 mol), and triethylbenzylammonium chloride (0.23 g, 0.001 mmol) in benzene (25 mL). The temperature of the reaction mixture rose from 20 to 30°C. The mixture was stirred for 30 min at 60°C, then cooled to room temperature, and benzene (40 mL) and water (40 mL) were added. The organic layer was separated, washed with water (30 mL), dried with sodium sulfate, and evaporated under reduced pressure. The residue was treated with ether (100 mL) and the triphenylphosphine oxide was separated. The ether solution was evaporated, the residue was distilled in vacuo and the middle distillate was collected. Yield 4 g (47%).

The decarboxylation of the trihaloacetic acid salts **191** is accompanied by the formation of dihalocarbenes, which, in the presence of tertiary phosphines, give phosphorus ylides **192**; the latter enter into the Wittig reaction with carbonyl compounds (Eq. 4.136)[403,404,411–415]. An improvement of this method involves the reaction of triphenylphosphine with methyl chlorodifluoroacetate in the presence of lithium chloride that presumably proceeds via the formation of difluorocarbene (Eq. 4.137,138)[416–419]:

$$\underset{\mathbf{191}}{ClCF_2CO_2M} \xrightarrow[-MCl,\ -CO_2]{} [CF_2:] \xrightarrow{R_3P} \underset{\mathbf{192}}{R_3P{=}CF_2} \xrightarrow{RCHO} RCH{=}CF_2 \qquad (4.136)$$

M=Li, Na, K, SnMe3; R= Bu, Ph

$$\mathrm{CFCl_2CO_2Me} \xrightarrow[\mathrm{Ph_3P}]{\mathrm{MeONa/MeOH}} \mathrm{Ph_3P{=}CClF} \xrightarrow{\mathrm{RCHO}} \mathrm{RCH{=}CFCl} \qquad (4.137)$$

$$\mathrm{ClCF_2CO_2Me} \xrightarrow{\mathrm{LiCl}} \mathrm{Cl_2CFCO_2Li} \xrightarrow[\mathrm{-LiCl,\ -CO_2}]{\mathrm{Ph_3P}} \mathrm{Ph_3P{=}CClF} \qquad (4.138)$$

Heating of triphenylphosphine with dichlorofluoromethyl(phenyl) mercury, the source of chlorofluorocarbene, yields triphenylphosphonium chlorofluoromethylide **189** (Eq. 4.139)[420]:

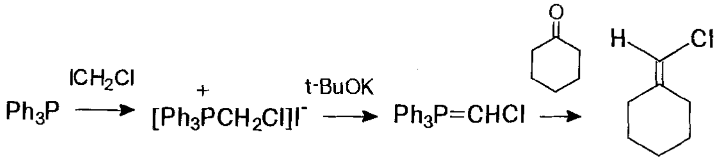
$$\mathrm{Ph_3P} + \mathrm{PhHgCFCl_2} \xrightarrow[\mathrm{xylol}]{80^{\circ}\mathrm{C}} \underset{\mathbf{189}}{\mathrm{Ph_3P{=}CFCl}} + \mathrm{PhHgCl}. \qquad (4.139)$$

Sometimes reaction occurs without the formation of a dihalocarbene. For instance, sodium dichlorofluoroacetate reacts with tertiary phosphines to give betaines which are converted by decarboxylation into triphenylphosphonium chlorofluoromethylide **189** (Eq. 4.140) [404,405,412]:

$$\mathrm{Ph_3P} + \mathrm{Cl_2CFCO_2Na} \xrightarrow[\mathrm{-NaCl}]{} [\mathrm{Ph_3\overset{+}{P}CFClCO_2^-}] \xrightarrow[\mathrm{-CO_2}]{} \underset{\mathbf{189}}{\mathrm{Ph_3P{=}CFCl}} \qquad (4.140)$$

The C-halogen-substituted phosphorus ylides **194** have been obtained by dehydrohalogenation of halomethyltriphenylphosphonium salts **193** by butyl- or phenyllithium, lithium diisopropylamide, or potassium *tert*-butoxide (Eq. 4.141, 4.142) [379,421–432]:

$$\mathrm{Ph_3P} + \mathrm{CH_2FI} \longrightarrow \underset{\mathbf{193}}{[\mathrm{Ph_3\overset{+}{P}CH_2F}]\mathrm{I}^-} \longrightarrow \underset{\mathbf{194}}{\mathrm{Ph_3P{=}CHF}} \qquad (4.141)$$



(4.142)

Chloromethylenecyclohexane (Eq. 4.142)[432a]

(a) A solution of triphenylphosphine (15.7 g, 60 mmol) in THF (100 mL) was placed in a round-bottomed flask, chloroiodomethane (13.5 g 75 mmol) was added dropwise with stirring, and the solution was heated under reflux for 15–20 h. The reaction mixture was then cooled and the colorless precipitate was removed by filtration and washed with ether. The phosphonium salt was dried under vacuum and used for the next synthesis.

(b) Absolute *tert*-butyl alcohol (12.5 mL) was placed in a three-necked round-bottomed flask equipped with stirrer bar and condenser. Potassium (0.6 g, 15 mmol) was added and the mixture was heated under reflux for 1–1.5 h (until the potassium had dissolved) to afford a solution of potassium *tert*-butoxide. Chloromethyl-triphenylphosphonium iodide (5.5 g, 12.5 mmol) was then added to the flask and the reaction mixture was stirred at room temperature for 1–1.5 h. A solution of cyclohexanone (1.0 g, 10 mmol) in *tert*-butanol (5 mL) was added dropwise over a period of 15–20 min to maintain the reaction temperature 15–20°C and the reaction mixture was then stirred for 4 h at 20°C. The reaction mixture was then diluted with water (25 mL) and extracted with pentane (3 x 25 mL). The extract was washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was distilled to give the desired product. Yield 94%.

Butyl- and phenyllithium not only deprotonate the phosphonium salt, but can also lead to exchange of the halogen atoms on the *a* carbon for lithium[421–432] or a butyl group[142], giving rise to a mixture of ylides **194** and **195** (Eq. 4.143; 4.144). A mixture of alkenes was formed in the subsequent reaction with carbonyl compounds.

$$\mathrm{Ph_3\overset{+}{P}CH_2X]X^-} \xrightarrow{\mathrm{PhLi}} \mathrm{Ph_3P{=}CHX} + \mathrm{Ph_3P{=}CH_2} \qquad (4.143)$$

$\mathrm{X{=}Br,\ Cl,\ I}$

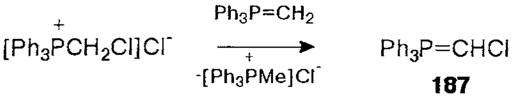
$$\mathrm{Ph_3\overset{+}{P}CH_2F]I^-} \xrightarrow{\mathrm{BuLi}} \underset{\mathbf{194}}{\mathrm{Ph_3P{=}CHF}} + \underset{\mathbf{195}}{\mathrm{Ph_3P{=}CHBu}} \xrightarrow{\mathrm{R_2C{=}O}} \mathrm{R_2C{=}CHF} + \mathrm{R_2C{=}CHBu} \qquad (4.144)$$

The capacity of triphenylphosphonium halomethylides to react with organolithium compounds increases in the order Cl < Br < I[429–432]. The substitution of butyl- or phenyllithium by a sterically hindered sodium bis(trimethylsilyl)amide enables elimination of side-reactions[423,424].

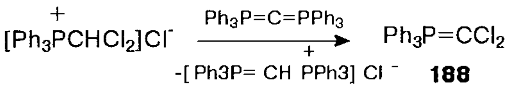
2-Iodoethenylcyclohexane[424]

A solution (1 N) of sodium bis(trimethylsilyl)amide in THF (1 mL) was added slowly, dropwise to a suspension of iodomethyltriphenylphosphonium iodide (0.55 g, 0.001 mol) in THF (2–3 mL) at room temperature. The reaction solution was stirred for 2–3 min, cooled to -60°C and HMPTA (0.3 mL) was added. The reaction mixture was then cooled to –78°C and cyclohexanecarboxaldehyde (0.1 mL, 0.0008 mol) was added. The reaction mixture was warmed to room temperature, stirred for 0.5 h at this temperature, and then mixed with hexane (20 mL). The precipitate was removed by filtration, the solvent was evaporated, and the residue was purified by column chromatography over silica gel The desired product was obtained in 71% yield and 15.1:1 *Z:E* ratio.

The dehydrohalogenation of chloromethyltriphenylphosphonium chloride by unstabilized phosphorus ylides, e.g. triphenylphosphonium methylide, occurs very smoothly without side-reactions and gives pure triphenylphosphonium chloromethylide **187** in the form of orange crystals with high yields (Eq. 4.145)[423]. The dehydrochlorination of dichloromethyltriphenylphosphonium chloride by hexaphenylarbodiphosphorane in aprotic solvents gave dichloromethylide **188** exclusively (Eq. 4.146)[423,425]:



$$[Ph_3\overset{+}{P}CH_2Cl]Cl^- \xrightarrow[-[Ph_3\overset{+}{P}Me]Cl^-]{Ph_3P=CH_2} \underset{\mathbf{187}}{Ph_3P=CHCl} \qquad (4.145)$$

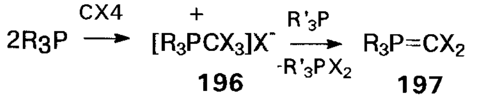


$$[Ph_3\overset{+}{P}CHCl_2]Cl^- \xrightarrow[-[Ph3P=CH\overset{+}{P}Ph3]\,Cl^-]{Ph_3P=C=PPh_3} \underset{\mathbf{188}}{Ph_3P=CCl_2} \qquad (4.146)$$

Triphenylphosphonium chloromethylide (Eq. 4.145)[423]

Triphenylphosphonium methylide (13.8 g, 0.05 mol) was added to chloromethyltriphenylphosphonium chloride (21 g, 0.06 mol) in absolute THF (300 mL) and the mixture was stirred for 20–30 min. The phosphonium salt was removed by filtration and the solvent was evaporated. The residue, an orange crystalline solid, was purified by crystallization from THF. Yield 10.9 g (70%), mp 95–98°C (dec.)

The dehydrohalogenation of trihalomethylphosphonium salts **196**[426,433–447], obtained by reaction of tertiary phosphines with tetrahalomethanes, is an important route for the synthesis of C-halogen-substituted phosphorus ylides[429–431,433]. The polyhalomethylphosphonium salts are dehalogenated by tertiary phosphines such as triphenylphosphine or tris(dimethylamino)phosphine (Eq. 4.147)[438–441]:



$$2R_3P \xrightarrow{CX4} \underset{\mathbf{196}}{[R_3\overset{+}{P}CX_3]X^-} \xrightarrow[-R'_3PX_2]{R'_3P} \underset{\mathbf{197}}{R_3P=CX_2} \qquad (4.147)$$

$CX_4 = CCl_4$[453c,453d], $CBrCl_3$. CBr_4[453e], CBr_2Cl_2[453b], CCl_2F_2[453c,457]

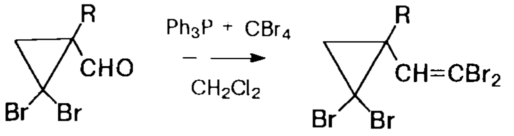
Triphenylphosphonium dibromomethylide (Eq. 4.147)

Triphenylphosphine (26.2 g, 0.1 mol) was added to a solution of carbon tetrabromide (16.6 g, 0.05 mol) in dichloromethane (250 mL) with good stirring, the temperature of reaction mixture being kept below 0°C. The orange solution of the ylide obtained was ready for olefination of carbonyl compounds. Addition to the ylide solution of benzaldehyde (5.3 g, 0.05 mol) gives 11.0 g (84%) of 1,1-dibromostyrene.

1,1-Dibromo-3-methyl-1-butene[478]

A solution of triphenylphosphine (42 g, 160 mmol) in dry dichloromethane (150 mL) was placed in a round-bottomed flask and zinc dust (10.5 g, 160 mmol) and carbon tetrabromide (53.1g, 160 mmol) in absolute dichloromethane (50 mL) were added consecutively at room temperature. The reaction mixture was then stirred for 24 h. A solution of 2-methylpropanal (5.76g, 80 mmol) in dichloromethane was added dropwise with stirring at 20°C and the mixture was stirred for 2 h at this temperature. The reaction solution was diluted with petroleum ether, centrifuged, the solution was evaporated, and the residue was purified by column chromatographed or distilled. Yield 58%.

This method has been successfully used for the synthesis of some natural biologically active compounds, e.g. for the preparation of dibromovinyl dibromocyclopropanes (Eq. 4.148)[426,441]:



(4.148)

This method has also been used for the preparation of phosphonium dichloromethylides immobilized on a polymer carrier (Eq. 4.149)[448]:

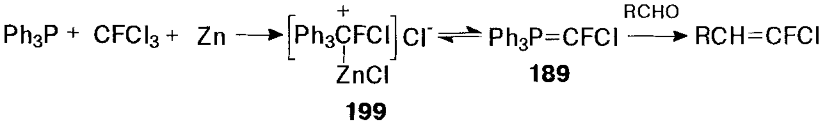
$$\textcircled{P}\!-\!PPh_2 \xrightarrow{CCl_4} [\textcircled{P}\!-\!\overset{+}{P}(Ph_2)Cl]\;\overset{-}{C}Cl_3 \longrightarrow \textcircled{P}\!-\!P(Ph_2)=CCl_2 \qquad (4.149)$$

The reaction of triphenylphosphine with tetrahalomethanes may be accompanied by the formation of ylide-phosphonium salts **198** (X = Cl, F), which are used for the preparation of haloketones (Eq. 4.150)[442–445]:

$$\underset{R=Bu,\ Ph}{R_3P} \xrightarrow{CXCl_3} Ph_3P=CXCl + Ph_3PCl_2 \xrightarrow{Ph_3P} \underset{\textbf{198}}{[R_3P=CX\overset{+}{P}R_3]Cl^-} \qquad (4.150)$$

Burton and Van Hamme have proposed the dehalogenation of polyhalomethylphosphonium salts by the Group IIB metals (zinc, cadmium, or mercury)[456]. This procedure gives an organometallic phosphonium salt **199**, which dissociates to form a metal chloride and the phosphorus ylide **189**; the latter readily enters into the Wittig reaction with aldehydes and ketones. (Eq. 4.151)[431].:

Heating of triphenylphosphine with chlorotrifluoromethane in the presence of zinc results in the formation of quasi-complex organometallic compounds, which were isolated in the individual form. These organometallic complexes are surprisingly stable in ethereal solution. The zinc complex, for example, retains it olefination capacity for a month. They do, however, react readily with aldehydes, ketones and activated esters to furnish the corresponding olefins in high yield. Analogously, triphenylphosphine reacts with fluorodiiodomethane to give a stable fluoroiodomethyltriphenylphosphonium iodide, which is converted into triphenylphosphonium fluoromethylide **194** under the action of a zinc–copper couple (Eq. 4.152)[142,427]

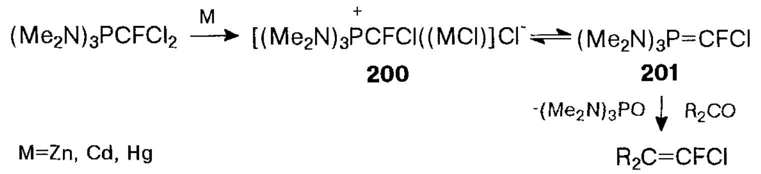


$$Ph_3P + CFCl_3 + Zn \longrightarrow [Ph_3\overset{+}{C}FCl(ZnCl)]Cl^- \rightleftharpoons \underset{\mathbf{189}}{Ph_3P{=}CFCl} \xrightarrow{RCHO} RCH{=}CFCl \quad (4.151)$$

199

$$Ph_3P + CHFCl_2 \longrightarrow [Ph_3PCHFI]I^- \xrightarrow{Zn/Cu,\ 0^o} \underset{\mathbf{194}}{Ph_3P{=}CHF} \quad (4.152)$$

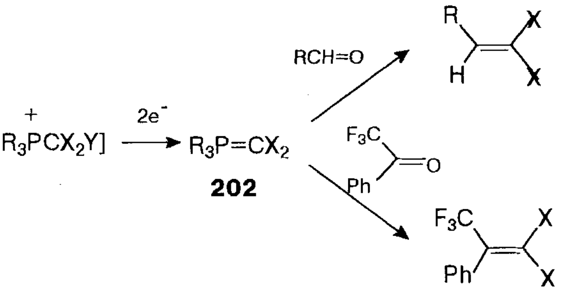
NMR Studies have demonstrated that the reaction of a trihalomethylphsphonium salt with zinc gives the organozinc complex **200**, which dissociates to $ZnCl_2$ and the phosphorus ylide **201**[383]. Although the equilibrium is strongly shifted towards the complex **200**, a Wittig reaction occurs in the presence of a carbonyl compound, which is evidence for the formation of the ylide **201** (Eq. 4.153)[414,426]:



$$(Me_2N)_3PCFCl_2 \xrightarrow{M} \underset{\mathbf{200}}{[(Me_2N)_3\overset{+}{P}CFCl((MCl)]Cl^-} \rightleftharpoons \underset{\mathbf{201}}{(Me_2N)_3P{=}CFCl} \xrightarrow[-(Me_2N)_3PO]{R_2CO} R_2C{=}CFCl \quad (4.153)$$

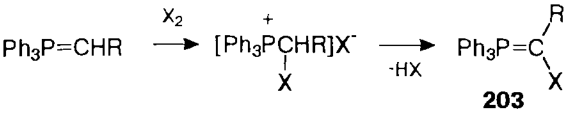
M=Zn, Cd, Hg

Collignon and coworkers have applied an electrochemical technique for the synthesis of C-halogen-substituted phosphorus ylides. The two-electron electrochemical reduction of dihalo- and trihalomethylphosphonium salts in acetonitrile led to the phosphorus ylides **202**, which enter into the Wittig reaction with aldehydes and reactive ketones in aprotic media (DMF or acetonitrile) to yield the corresponding haloalkenes (Scheme 4.26)[443]:



Scheme 4.26

The C-halogen-substituted phosphorus ylides **203** have been synthesized by halogenation of phosphorus ylides with hydrogen atoms on the ylide carbon atom (Eq. 4.154). For ylides containing strong electron acceptors on the *a* carbon atom (R = CO_2Alk, C(O)Alk, C(O)Ar), the dehydrochlorination of the intermediate phosphonium salt is performed in the presence of triethylamine[447]. Chlorine, bromine[447], iodine[95], phenyliododichloride[448], and chloramine T[449,450] have been used as halogenating agents.



$$\mathrm{Ph_3P{=}CHR \xrightarrow{X_2} [Ph_3\overset{+}{P}\underset{\substack{|\\ X}}{C}HR]X^- \xrightarrow[-HX]{} Ph_3P{=}C\begin{smallmatrix}R\\ X\end{smallmatrix}} \tag{4.154}$$

203

Triphenylphosphonium alkoxycarbonyl-bromomethylide **203** *($R=CO_2Me$, $X=$ Br) (Eq. 4.154)*[447b]

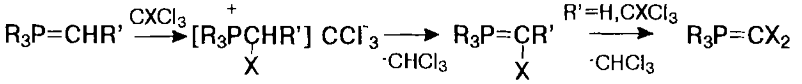
A solution of bromine (10 mmol) in chloroform (10 mL) was added to a solution of triphenylphosphonium alkoxycarbonylmethylide (10 mmol) and triethylamine (11 mmol) in chloroform (25 mL). The triethylamine chlorohydrate was removed by filtration, the solvent was evaporated, and the residue was recrystallized from aqueous alcohol. Yield 96%, mp 166–168°C.

The unstabilized phosphorus ylides are halogenated by perhalofluoroalkanes. The reaction occurs regioselectively and high yields of α-haloalkylphosphonium salts are obtained[451]. The fluorination of triphenylphosphonium methylide by $FClO_3$ followed by treatment with NaI gives the fluoromethylphosphonium salt which, on dehydroiodination, gives the triphenylphosphonium fluoromethylide **194** in high yield; this ylide enters into the Wittig reaction with aldehydes to form vinylfluorides (Eq. 4.155)[452].

$$\mathrm{Ph_3P{=}CH_2 \xrightarrow{FClO_3;\ NaI} [Ph_3\overset{+}{P}CH_2F]I^- \xrightarrow{PhLi} Ph_3P{=}CHF} \tag{4.155}$$

194

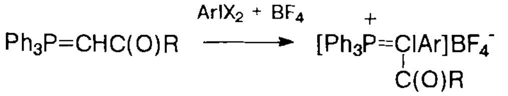
Exchange of a hydrogen atom on the ylide carbon atom for chlorine or bromine occurs when phosphorus ylides react with carbon tetrachloride and carbon tetrabromide (Eq. 4.156)[473,474]:



$$\mathrm{R_3P{=}CHR' \xrightarrow{CXCl_3} [R_3\overset{+}{P}\underset{\substack{|\\ X}}{C}HR']\ CCl_3^- \xrightarrow[-CHCl_3]{} R_3P{=}\underset{\substack{|\\ X}}{C}R' \xrightarrow[-CHCl_3]{R'=H,CXCl_3} R_3P{=}CX_2} \tag{4.156}$$

X=Br, Cl

The phosphonium-iodonium ylides **204** have been prepared by reaction of stabilized phosphorus ylides with derivatives of trivalent iodine (Eq. 4.157)[455]:



$$\mathrm{Ph_3P{=}CHC(O)R \xrightarrow{ArIX_2\ +\ BF_4} [Ph_3\overset{+}{P}{=}\underset{\substack{|\\ C(O)R}}{C}IAr]BF_4^-} \tag{4.157}$$

204

X_2=O, F_2, $(OMe)_2$; Ar=Ph, 2-MeC_6H_4; R=EtO, Ph, 4-MeC_6H_4

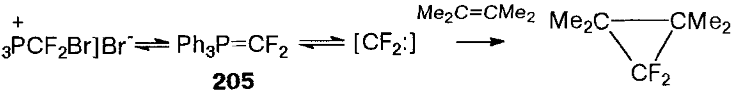
The halogen atom on the α-carbon atom of tertiary alkylphosphines is highly mobile, which determines its migration towards the phosphorus atom—the 1,2(C→P)-halotropic shift. α-Haloalkylphosphines containing electron-accepting substituents on the α carbon atom rearrange rather readily into phosphorus ylides, and the halogen atom in such ylides can be substituted by various substituents (See Section 5.3.3.1). Numerous examples of the preparation of phosphorus ylides by this method have been described [12,456-463]:

Properties

C-halo-substituted phosphorus ylides have been studied in detail using quantum-chemical calculations and physicochemical methods. Ab initio quantum-chemical calculations performed by Dixon[464] and by Bestmann[16] have shown that the C-fluorine-containing ylide $H_3P{=}CHF$ has a non-planar P=CHF group with an inversion barrier of approximately 2.8 kcal mol^{-1}. Francl et al.[465] assumed, in accordance with Dixon's results, that the zwitterionic character of the P=C bond in the $H_3P{=}CF_2$ molecule is minimal and on the basis of electron-density differences concluded that introduction of a fluorine atom to the α carbon atom enhances the π character of the P=C bond.

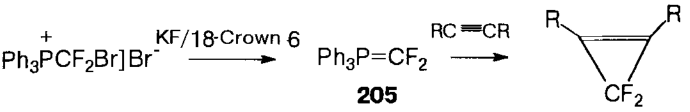
Because of hindered rotation around the P=C bond, as a result of partial enolization and a considerable shift of negative charge to the carbonyl oxygen atom, alkoxycarbonyl- and acylfluoromethylides exist as mixtures of two geometric isomers[421].

The stability of C-halogen-containing phosphorus ylides depends on the electron-accepting properties of the second substituent on the ylide carbon atom. C-Haloylides stabilized by strong electron-accepting substituents can be isolated and purified, whereas non-stabilized ylides with one or two halogen atoms on the α carbon atom are unstable and are thus usually used in subsequent reactions without isolation and purification[423,425]. Only triphenylphosphonium chloromethylide[423] and -dichloromethylide[426] have been isolated in pure state. All attempts to isolate fluoromethylides **189**, **192**, and **194** have been unsuccessful and these ylides have not been detected by NMR spectroscopy. Triphenylphosphonium difluoromethylide **205**, which has been prepared by the reaction of bromodifluoromethyltriphenylphosphonium bromide with tertiary phosphines or with potassium fluoride in the presence of 18-crown-6 dissociates readily into difluorocarbene and triphenylphosphine. Difluorocarbene has been captured by tetramethylethylene. The formation of 1,1-difluoro-2,2,3,3-tetramethylcyclopropane in solution indicated the presence of difluorocarbene (Eq. 4.159)[466]:



(4.158)

Schlosser and coworkers[467] have recently demonstrated that difluoromethylide **205** adds to mono- and disubstituted acetylenes to give difluorocyclopropenes in good yield (Eq. 4.159):



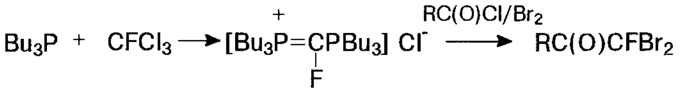
205

(4.159)

The alkylation, acylation, and arylation of simple fluoromethylides leads directly to C-substituted fluoromethylides, as a result of transylidation, and presents a convenient synthetic route to various fluoroalkenes (Eq. 4.160)[447]:

$$\mathrm{Ph_3P{=}CCl_2 \xrightarrow{R'C(O)Cl} Ph_3P{=}CClC(O)R' \xrightarrow{R''CHO} R''CH{=}CClC(O)R'} \qquad (4.160)$$

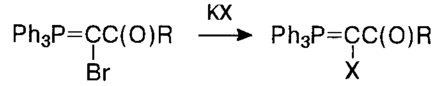
The acylation of C-fluoro-substituted ylides **206**, obtained by the reaction of tributylphosphine with trichlorofluoromethane and then bromination, is a convenient means of preparing haloalkyl ketones (Eq. 4.161)[445]:



$$\mathrm{Bu_3P + CFCl_3 \longrightarrow [Bu_3\overset{+}{P}{=}\underset{\displaystyle F}{\underset{|}{C}}PBu_3]\,Cl^- \xrightarrow{RC(O)Cl/Br_2} RC(O)CFBr_2} \qquad (4.161)$$

206

Reaction of C-bromo-substituted ylides with potassium iodide or thiocyanate results in substitution of the bromine atom on the ylide carbon atom by iodine or a thiocyano group (Eq. 4.162)[447,469]:



$$\mathrm{Ph_3P{=}\underset{\displaystyle Br}{\underset{|}{C}}C(O)R \xrightarrow{KX} Ph_3P{=}\underset{\displaystyle X}{\underset{|}{C}}C(O)R} \qquad (4.162)$$

X=I, SCN

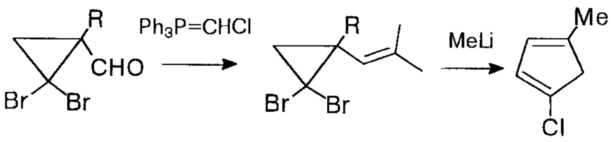
α-Haloalkylphosphines exist in tautomeric equilibrium with ylides containing the halogen on the phosphorus atom and therefore manifest chemical properties characteristic of both trivalent phosphorus and ylides.[469–472]:

The C-halogen-substituted phosphorus ylides are valuable reagents for the synthesis of haloalkenes. Because electron-accepting halogen atoms on the ylide carbon atom reduce the nucleophilicity of the phosphorus ylides, triphenylphosphonium haloylides readily alkenate aldehydes and activated ketones, and do not alkenate non-activated ketones and carboxylic esters. The reactivity of haloylides can be enhanced by introducing electron-donating substituents, e.g. dimethylamino groups, on the phosphorus atom; these reduce the electrophilicity of the phosphonium group.

Tris(dialkylamino)phosphonium ylides have definite advantages as haloalkenating reagents over the triphenylphosphonium ylides. For instance, tris(dimethylamino) phosphonium dichloromethylide **207** converts ethyl-*cis*-*trans*-caronaldehyde into chrysanthemic acid in high yield; this could not be achieved with triphenylphosphonium ylide **187** (Eq. 4.163)[433,437–439]:

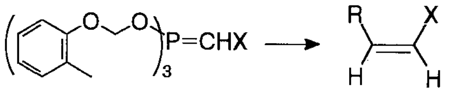
$$(Me_2N)_3P \xrightarrow{BrCCl_3/-76^\circ C} \underset{\mathbf{207}}{(Me_2N)_3P{=}CCl_2} \xrightarrow{Me_2CHCHO} Cl_2C{=}CHCHMe_2 \qquad (4.163)$$

Halovinyl-substituted dibromocyclopropanes, the initial compounds in the synthesis of cyclopentadienes, and alkenes, have been obtained from triphenylphosphonium chloromethylide (Eq. 4.164)[441]:



(4.164)

Schlosser has proposed a highly stereoselective method for the synthesis of haloalkenes which involves 2-methoxymethoxyphenylphosphonium ylides **208** instead of triphenylphosphonium ylides. In this case, the *cis*-*trans* isomer ratio of alkenes **209** was 98:2–99:1 (Eq. 4.167)[497]:



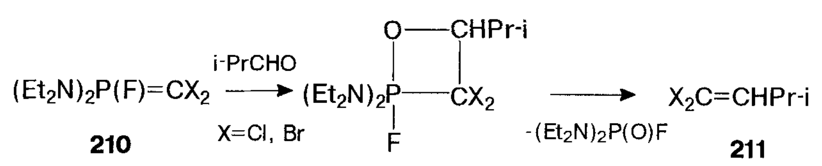
208

X = Cl, Br, I

209

(4.165)

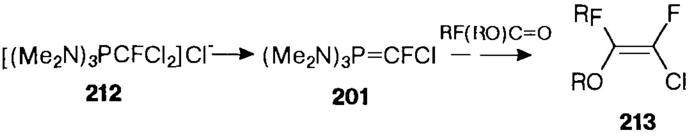
The reaction of aldehydes with ylide **210** containing a fluorine atom on the phosphorus atom yielded the four-membered cycloadducts of the Wittig reaction, **211**, which have been isolated. On heating to 60–80°C, the adducts decomposed into 1,1-dihaloalkenes and bis(diethylamino)phosphoryl fluoride (Eq. 4.166)[473]:



210 **211**

(4.166)

The reaction of tris(dimethylamino)phosphonium chlorofluoromethylide **201** with fluoroalkylcarboxylic esters is stereoselective and occurs with the predominant formation of *Z* isomers of alkyl polyfluoroalkenyl ethers **213** (Eq. 4.167):

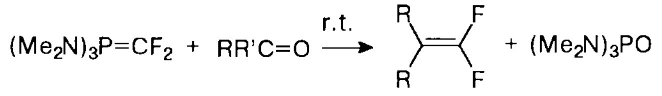


212 **201** **213**

(4.167)

Monofluoro-, fluorochloro-, and bromofluoromethylides, however, usually react with aldehydes and asymmetrical ketones to give mixtures of *Z* and *E* alkenes[36,36]. The yields and the stereochemistry of the Wittig reaction with tris(dimethylamino) phosphonium haloylides depend on the method of dechlorination of the phosphonium salt. A high yield of *Z*-1-chloro-2-propoxyperfluoropropene is achieved by dechlorination of salt **212** with tris(dimethylamino)phosphine in the presence of isopropyl trifluoroacetate[426,433–436]. The zinc–copper couple exothermally dehalogenated phosphonium salts **212** in the presence of carbonyl compounds $R^1R^2C=O$ (R^1 = Ph, C_6H_{13}, CF_3; R^2 = H, Ph, CF_3, Me, AlkO), with the formation of 1-chloro-1-fluoroalkenes. The yields of alkenes from aldehydes and activated ketones are almost quantitative, whereas for ketones of the acetophenone type the yields are approximately 70%.

The difluoromethylide **214**, which is generated from tris(dimethylamino) phosphine and dibromofluoromethane, is a convenient source of the difluoromethylene group; **214** enters into the Wittig reaction with cyclohexanone, acetophenone, propiophenone, uridinons (Eq. 4.168)[433,435,436]:

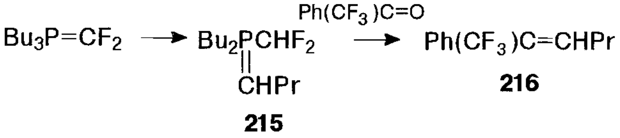


214

(4.168)

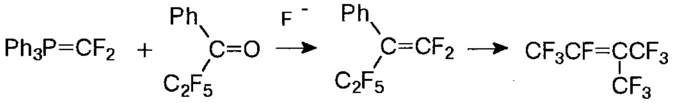
Triphenylphosphonium fluoromethylide **194** olefinates aliphatic and aromatic aldehydes, and activated and non-activated ketones[142,428]. Triphenylphosphonium fluorochloromethylide **187** generated by reaction of triphenylphosphine with sodium dichlorofluoroacetic acid enters into the Wittig reaction with aldehydes and activated ketones to yield 1:1 mixtures of *Z* and *E* alkenes in 1:1 ratio[142,428], and alkenates aromatic α-oxocarboxylic esters with formation of α-aryl chlorofluoroacrylic acids.[403,404,416,417,474–476] Triphenylphosphonium difluoromethylide **205** converts aldehydes and activated ketones into α,α-difluoroolefins in high yields; it does not, however, olefinate cyclohexanone or acetophenone because of their insufficient electrophilicity. Tributylphosphonium difluoromethylide is highly reactivity owing to the electron-donating effect of the butyl groups. This ylide, generated by the haloacetate method, olefinates in situ such non-activated ketones as benzophenone, cyclohexanone, and methylketones RC(O)Me where R = C_5H_{11}, Ph, 2-furyl, 2-thienyl, etc[416,417]. Examples of the Wittig reaction with C-fluorinated ylides can be found in the recently published review of D. Burton.[401b]

Examples are known of anomalies in the course of the Wittig reaction with tributylphosphonium difluoromethylide. For instance, in the reaction of tributylphosphonium difluoromethylide with trifluoroacetophenone, a prototropic rearrangement of the difluoro-methylide into the butylide **215** yields the alkene **216** (Eq. 4.169)[411,416]:

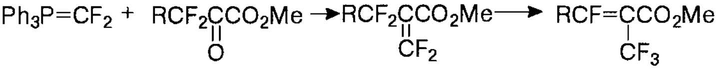


$$\mathrm{Bu_3P{=}CF_2} \longrightarrow \underset{\textbf{215}}{\underset{\mathrm{CHPr}}{\underset{\|}{\mathrm{Bu_2P}}}\mathrm{CHF_2}} \xrightarrow{\mathrm{Ph(CF_3)C{=}O}} \underset{\textbf{216}}{\mathrm{Ph(CF_3)C{=}CHPr}} \qquad (4.169)$$

The Wittig reaction of C-fluoro-substituted ylides with ketones containing perfluoroalkyl groups is sometimes accompanied by isomerization associated with migration of the fluorine atom from the perfluoroalkyl to difluoromethylene group (Eq. 4.170)[432]. The isomerization of fluoroalkenes is suppressed when the reaction is performed in the absence of strong bases or dehalogenating agents (Eq. 4.171)[411]:

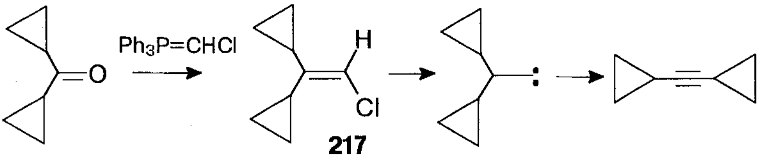


$$\mathrm{Ph_3P{=}CF_2} + \begin{array}{l}\mathrm{Ph}\\ \;\mathrm{C{=}O}\\ \mathrm{C_2F_5}\end{array} \xrightarrow{\mathrm{F^-}} \begin{array}{l}\mathrm{Ph}\\ \;\mathrm{C{=}CF_2}\\ \mathrm{C_2F_5}\end{array} \longrightarrow \mathrm{CF_3CF{=}}\underset{\mathrm{CF_3}}{\underset{|}{\mathrm{C}}}\mathrm{CF_3} \qquad (4.170)$$



$$\mathrm{Ph_3P{=}CF_2} + \mathrm{RCF_2}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{CO_2Me} \longrightarrow \mathrm{RCF_2}\underset{\mathrm{CF_2}}{\underset{\|}{\mathrm{C}}}\mathrm{CO_2Me} \longrightarrow \mathrm{RCF{=}}\underset{\mathrm{CF_3}}{\underset{|}{\mathrm{C}}}\mathrm{CO_2Me} \qquad (4.171)$$

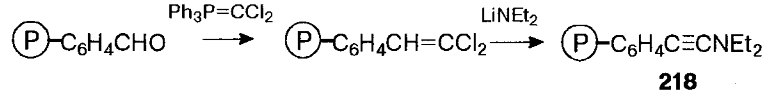
The reaction of triphenylphosphonium chloromethylide with dicyclopropyl ketone gives the chloroalkene **217** in 81% yield; it is transformed into dicyclopropyl-acetylene, which is formed via a carbenoid (Eq. 4.172)[477]:



217

(4.172)

Triphenylphosphonium dichloromethylide has been used for the modification of polymeric reagents, for instance, for the preparation of polymeric ynamines **218** (Eq. 4.173)[478]:

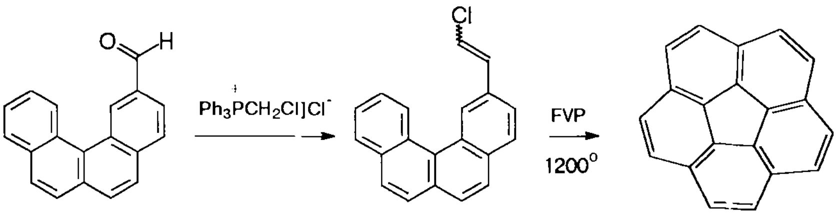


$$\textcircled{\scriptsize P}\!-\!\mathrm{C_6H_4CHO} \xrightarrow{\mathrm{Ph_3P{=}CCl_2}} \textcircled{\scriptsize P}\!-\!\mathrm{C_6H_4CH{=}CCl_2} \xrightarrow{\mathrm{LiNEt_2}} \underset{\textbf{218}}{\textcircled{\scriptsize P}\!-\!\mathrm{C_6H_4C{\equiv}CNEt_2}} \qquad (4.173)$$

Corey has proposed a convenient method for the synthesis of haloalkenes by reaction of triphenylphosphine with carbon tetrabromide in the presence of zinc dust[477]. The dibromomethylide **219** reacts in situ with aldehydes to form dibromoalkenes[474] that have been used in the synthesis of retinoids[474], alkynes[477], and alkynecarboxylic acids (Eq. 4.174)[339,426]:

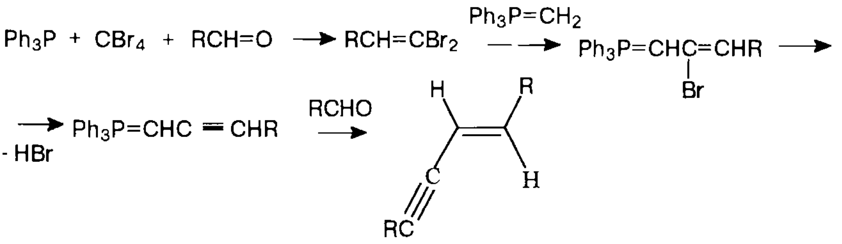
$$Ph_3P + CBr_4 + Zn \xrightarrow[CH_2Cl_2]{r.t.} \underset{\mathbf{219}}{[Ph_3P{=}CBr_2]} \xrightarrow{RCHO} RCH{=}CBr_2 \qquad (4.174)$$

A new synthesis of corannulene, a dominant structural motif of fullerene, was developed starting from the Wittig reaction of chloromethylide and arylaldehyde (Eq. 4.175)[477a]:



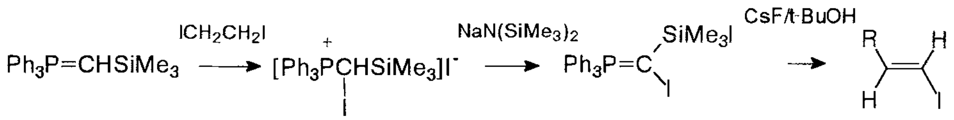
(4.175)

Bestmann has prepared synthons of pheromones on the basis of C-halogen-substituted ylides (Eq. 4.176)[479]:



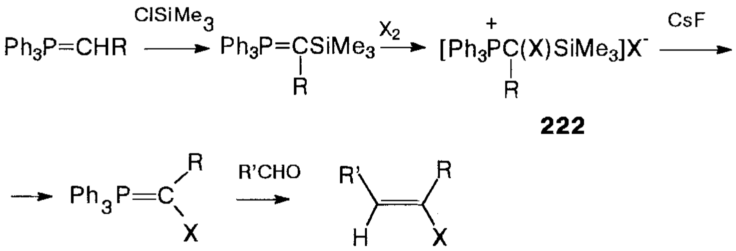
(4.176)

Methods for the preparation of α-haloalkenes on the basis of C-silicon-substituted ylides have been developed. The mild iodination of triphenylphosphonium trimethylsilylmethylide with 1,2-diiodoethane gives the iodoalkylphosphonium salt **220** in high yield. The dehydroiodination of **220** by sodium bis(trimethylsilyl)amide results in the formation of the trimethylsilyliodomethylide **221**, which is stereoselectively transformed into α-iodoalkenes on treatment with cesium fluoride in *tert*-butyl alcohol in the presence of carbonyl compounds (Eq. 4.177)[480]:



220 **221** (4.177)

The successive treatment of non-stabilised phosphorus ylides by chlorotrimethylsilane and halogen yields α-haloalkyl α-trimethylsilyltriphenylphosphonium salts **222**, their desilylation by cesium fluoride in the presence of aldehydes results in haloalkenes (Scheme 4.27).[481]



Scheme 4.27

Conclusion

Heteroatoms on the ylide carbon atom thus considerably affect the chemical properties and the reactivity of the phosphorus ylides. Certain heteroatoms, such as the atoms of the main Groups I and II, and nitrogen, tin, and lead atoms increase the electron density on the carbon atom and the reactivity of ylides while, in contrast, other heteroatoms such as silicon and germanium, Group V–VII atoms, and transition elements, stabilize the ylide carbanion, thus reducing its nucleophilicity. As a result, C-substituted phosphorus ylides acquire remarkable new chemical properties and offer new synthetic opportunities. This explains the deep interest of chemists in C-hetero-substituted phosphorus ylides as exceptionally promising reagents in organic synthesis[484].

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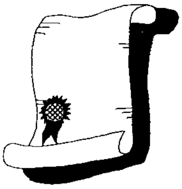

Phosphorus Ylides: Chemistry and Application in Organic Synthesis
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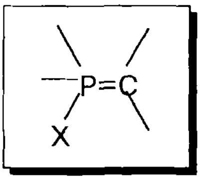
5

P-Heterosubstituted Phosphorus Ylides

This chapter is concerned with the synthesis and properties of phosphorus ylides substituted on the phosphorus atom of the P=C group with various heteroatoms. In recent years the chemistry of P-heteroatom-substituted (or, simply, P-heterosubstituted) phosphorus ylides has been extensively developed[1-5]. Ylides containing heteroatoms attached to the phosphorus atom have especially interesting and frequently unusual properties, because of different effects of the substituent heteroatoms on the distribution of the electron density in the molecule of these compounds.



$X = RO, R_2N, RS, Hlg, R_3Si, R_2P$, etc.

P-Heterosubstituted phosphorus ylides open a route to the preparation of many new types of organophosphorus compound to afford the possibility of interesting basic research into structure, reactivity, tautomeric transformations, and isomerization[3].

5.1 P–O Ylides

Alkoxyphosphonium ylides are the type of P–O phosphorus ylide studied in most detail. Ylides bearing ArO groups on the phosphorus are less studied. The characteristic feature of alkoxyphosphonium ylides is their tendency to dealkylate during both storage and chemical reactions. P–OAlk ylides are, therefore, less accessible than triphenylphosphonium ylides. P–O ylides cannot be prepared by traditional synthetic methods. They cannot be synthesized by the salt method because of the instability of the starting alkoxyphosphonium salts[3,9].

5.1.1 Synthesis

Several convenient routes to P-alkoxyylides have been developed[3]. These compounds are usually obtained by «oxidative ylidation» of phosphorus(III) compounds. The term «oxidative ylidation» implies reactions as a result of which the coordination number of the tervalent phosphorus atom increases and a P=C bond with a tetracoordinate phosphorus atom is formed[3,4].

5.1.1.1 The Oxidative Ylidation of CH Acids of Tervalent Phosphorus

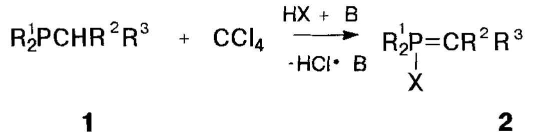
The «oxidative ylidation» of tervalent phosphorus compounds, in particular of tertiary phosphines and phosphonites containing a mobile hydrogen atom on the α carbon atom and behaving as CH acids of tervalent phosphorus, must be regarded as a general approach to the synthesis of P-heterosubstituted ylides.

Compounds **1** containing electron-acceptor substituents R^2 on the α carbon atom, thus increasing the mobility of the hydrogen atoms and stabilizing the ylide function, are ylidated very easily[5-6]. Often, however, successful ylidation of weak CH acids, for example, trialkylphosphines, is possible (Eq.5.1):

$$\underset{\mathbf{1}}{R_2PCHR_2} \xrightarrow{X} R_2P(X){=}CR_2 \xleftarrow[-H^+]{[CR_2]} R_2PX \qquad (5.1)$$

Phosphorus(III) CH acids are carbon analogs of phosphorus(III)OH acids, which can be converted into ylides in the same way as the OH acids of tervalent phosphorus[7-9]. In particular, phosphorus(III)CH acids undergo reactions resembling the Atherton–Todd, Michaelis–Backer, and Pudovik reactions characteristic of dialkyl phosphites. Certain alkylphosphines of type **1** isomerize to ylides with a P–H bond, analogous to the prototropic P(O)H forms of the phosphorus(III)OH acids; this emphasizes still further the similarity of these types of organophosphorus compound.

Depending on the structure of the initial tervalent phosphorus compounds, their ylidation can proceed via two pathways—either a substituent X is introduced on the phosphorus atom of compound **1**, with simultaneous deprotonation of the α carbon atom, or an alkylidene group is introduced in some way to the phosphorus atom of an X-substituted phosphine. Tertiary phosphines and phosphonites **1** containing electron-accepting substituents on the α carbon atom are ylidated upon reaction with carbon tetrachloride and alkylamines, aniline, or ammonia. (Eq.5.2, Table 5.1) The reaction models the Atherton–Todd reaction[12], according to which dialkyl phosphites react with carbon tetrachloride and alkylamines to form phosphoric acid amides[9-11].



$$\underset{\mathbf{1}}{R^1_2PCHR^2R^3} + CCl_4 \xrightarrow[-HCl\cdot B]{HX + B} \underset{\mathbf{2}}{R^1_2\underset{\displaystyle X}{\underset{|}{P}}{=}CR^2R^3} \qquad (5.2)$$

X=AlkO, PhO, AlkS, AlkNH, PhNH; CR^1R^2=$CHCO_2Et$, $CHSO_2CF_3$, $C(Ph)CO_2Et$, $C(CO_2Et)_2$, $C(SO_2Ph)$; B=Et_3N, Alk_2NH, $AlkNH_2$

Diethoxydiethylaminophosphonium bis(ethoxycarbonyl)methylide (**2**, R^1 = EtO, R^2 = R^3 = CO_2Et, X = Et_2N, Eq.1, Table 5.1)[9]

Carbon tetrachloride (3–4 mL) was added dropwise at 0°C to a solution of diethyl bis(ethoxycarbonyl) methylphosphonite (0.02 mol) and diethylamine (0.05 mol) in diethyl ether (15 mL) and the mixture was stirred for 20–30 min at room temperature. The diethylamine chlorohydrate was removed by filtration, the filtrate was evaporated to dryness, and the residue was distilled in vacuo. Yield 50%, bp 120°C (0.04 mm Hg), n_D 1.4682.

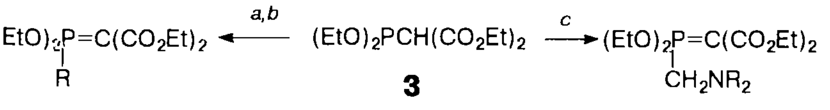
Diethyl diethylaminophosphonium trifluoromethylsulfonylmethylide (**2**, R^1 = Et, R^2 = SO_2CF_3, R^3 = H, X = Et_2N Eq.5.1, Table 5.1)[13]

Carbon tetrachloride (3–4 mL) was added dropwise at 0°C to a solution of diethyl(trifluoromethylsulfonyl) methylphosphine (0.02 mol) and diethylamine (0.05 mol) in ether (15 mL) and the mixture was stirred for 20–30 min. Diethylamine chlorohydrate was removed by filtration, the solvent was evaporated, and the residue was purified by low-temperature crystallization from ether. Yield 65%, mp 45–46°C (colorless prisms).

Table 5.1 Ylide Version of the Todd-Atherton Reaction (Eq.2)

R^1	R^2	R^3	X	Yield of **2**,%	Ref
EtO	CO_2Et	CO_2Et	H_2N	68	13,5
EtO	CO_2Et	CO_2Et	Et_2N	50	13
i-PrO	CO_2Et	CO_2Et	i-PrNH	75	13
EtO	CO_2Et	CO_2Et	PhNH	10,55	13,16
Et	CO_2Et	CO_2Et	EtO	70	5
EtO	CO_2Et	CO_2Et	MeO	-	5
EtO	CO_2Et	CO_2Et	EtO	30	13
i-PrO	CO_2Me	CO_2Me	i-PrO	75	5
i-PrO	CO_2Et	CO_2Et	i-PrO	45	13
i-PrO	CO_2Et	CO_2Et	MeNH	70	13
i-PrO	CO_2Et	CO_2Et	Et_2N	70	13
i-PrO	CO_2Et	CO_2Et	EtS	40	13
i-PrO	CO_2Me	Ph	MeNH	45,70	5,17
i-PrO	CO_2Et	Ph	Et_2N	45	17
i-PrO	CO_2Et	H	MeNH	70	17
i-PrO	CO_2Et	H	Me_2N	28	17
Et	SO_2CF_3	H	Et_2N	65	6,14,15
Ph	SO_2Ph	SO_2Ph	Et_2N	40	10
Ph	SO_2Ph	SO_2Ph	PhO	65	10

Diethyl bis(ethoxycarbonyl)methylphosphonite **3** reacts with acetyl chloride in the presence of bases (Scheme 5.1, direction *a*)[18,19], with α-chloroesters under conditions of the Arbusov reaction (Scheme 5.1, direction *b*)[20], and with aminomethylenes under the conditions of the Kabachnik–Fields reaction (Scheme 5.1, direction *c*)[21]:

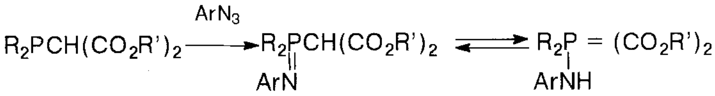


$$EtO)_2\underset{R}{P}=C(CO_2Et)_2 \xleftarrow{a,b} \underset{\mathbf{3}}{(EtO)_2PCH(CO_2Et)_2} \xrightarrow{c} (EtO)_2\underset{CH_2NR_2}{P}=C(CO_2Et)_2$$

a=MeC(O), *b*= $ROCH_2$; c=$CH_2(NR_2)_2$

Scheme 5.1

Compounds of tervalent phosphorus with a mobile hydrogen atom on the α carbon atom a converted into ylides by reactions involving prototropic rearrangement. The Staudinger imination of bis(alkoxycarbonyl)methylphosphines and the analogous phosphonites by aryl azides yields the phosphazo compounds **4**, which readily rearrange to give ylides, **5**, with an RNH group on the phosphorus[22] (phosphazo–ylide tautomerism) (Eq.5.3)[22]. The driving force of this rearrangement is the shift of the system towards the least «acid» tautomer.



$$R_2PCH(CO_2R')_2 \xrightarrow{ArN_3} \underset{\substack{\| \\ ArN}}{R_2P}CH(CO_2R')_2 \rightleftharpoons \underset{\substack{| \\ ArNH}}{R_2P} = (CO_2R')_2 \qquad (5.3)$$

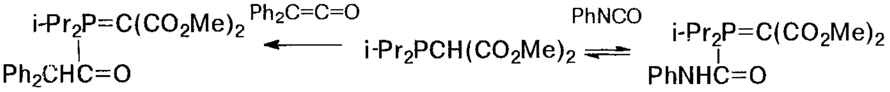
4 **5**

R=Et, EtO, i-PrO; R'=Me, Et; Ar=Ph, 4-$O_2NC_6H_4$

p-Nitrophenylamino(diisopropoxy)phosphonium bis(carboethoxy)methylide (Eq.5.3, Ar = 4-$O_2NC_6H_4$)

A solution of *p*-nitrophenylazide (0.025 mol) in ether (10 mL) was added dropwise, with stirring and cooling to 0°C, to a solution of diisopropyl dicarboethoxymethylphosphonite (0.025 mmol) in absolute ether (10 mL). The reaction mixture was then stirred for 50–60 min at room temperature, the solvent was evaporated, and the residue was purified by crystallization from hexane. Yield 60%, mp 124°C (yellow needles).

Phenyl isocyanate and diphenylketene readily add to C-phosphorylated malonic ester to produce P-acyl-substituted ylides **6**,**7** (Scheme.5.2)[6,7]. Ylides **7** are stable in the crystalline state but in solution dissociate to the initial compounds.

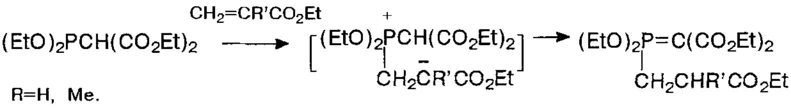


$$\underset{\substack{| \\ Ph_2CHC=O}}{i\text{-}Pr_2P}=C(CO_2Me)_2 \xleftarrow{Ph_2C=C=O} i\text{-}Pr_2PCH(CO_2Me)_2 \overset{PhNCO}{\rightleftharpoons} \underset{\substack{| \\ PhNHC=O}}{i\text{-}Pr_2P}=C(CO_2Me)_2$$

6 **7**

Scheme 5.2

Diethyl bis(ethoxycarbonyl)methylphosphonite reacts with acrylic and methacrylic acid esters under the conditions of the Pudovik reaction with the formation of ylides **8**[25]. In the presence of alkaline catalysts the yields of ylides and reaction rates are increased (Eq.5.4):



$$(EtO)_2PCH(CO_2Et)_2 \xrightarrow{CH_2=CR'CO_2Et} \left[\underset{\substack{| \\ CH_2\bar{C}R'CO_2Et}}{(EtO)_2\overset{+}{P}}CH(CO_2Et)_2\right] \longrightarrow \underset{\substack{| \\ CH_2CHR'CO_2Et}}{(EtO)_2P}=C(CO_2Et)_2 \qquad (5.4)$$

R=H, Me.

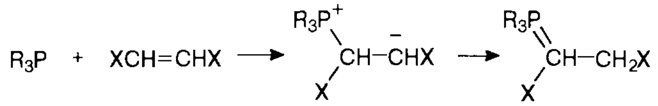
3 **8**

5.1.1.2 Reaction of Alkenes and Alkynes with Phosphites

Compounds with an activated multiple bond react readily with tervalent phosphorus compounds, often giving rise to P-ylides with phenyl, alkoxy, and dialkylamino groups on the phosphorus.

a) ***Reaction with Alkenes***

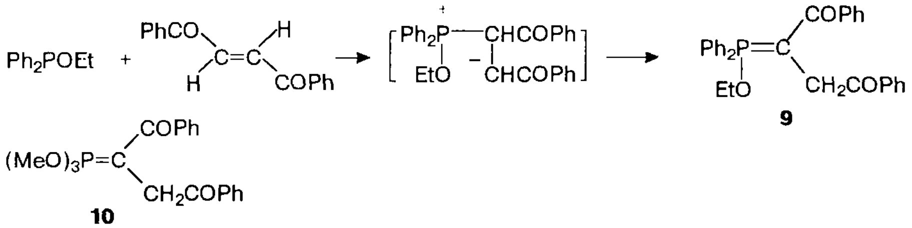
Nucleophilic attack by a tervalent phosphorus atom on the electron-unsaturated carbon atom of an activated multiple bond produces a very reactive betaine, which rearranges readily to an ylide. In the presence of an electron-accepting substituent X, the rearrangement of the betaine (A) to its less «acid» prototropic form (B), namely the ylide, proceeds readily (Eq.5.5):



A **B**

(5.5)

In 1966 Ramirez[26] showed that addition of ethyl diphenylphosphonate to *trans*-dibenzoylethylene results in an ylide with and ethoxy group on the phosphorus. **9** (Scheme 5.3). Electron-accepting phenacyl groups, which increase the mobility of the α proton, facilitate the rearrangement of the betaine to its less acidic ylide prototropic form. Ylide **10**, with three methoxy groups on the phosphorus, was obtained analogously.

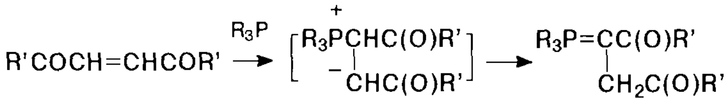


9

10

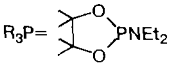
Scheme 5.3

Esters of trivalent phosphorus acids add readily to maleimides, fumaric acid esters, and *trans*-dibenzoylethylene with the formation of ylides **11** (Eq.5.6)[27,28]:



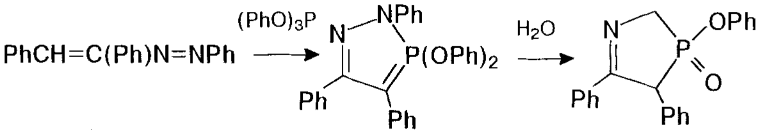
((5.6)

11



R=Ph, EtO; R=NH, NAr

Ylides **6** with phenoxy groups on the phosphorus atom have been obtained as a result of [1+4]-cycloaddition of triphenyl phosphite to a conjugated azoalkene. Ylide **12** is very hygroscopic and is formed as a colorless solid product only after complete removal of traces of moisture from the reaction mixture. The ylide hydrolyzes very easily to produce the diazaphosphole **13** (Eq.5.7)[29]:

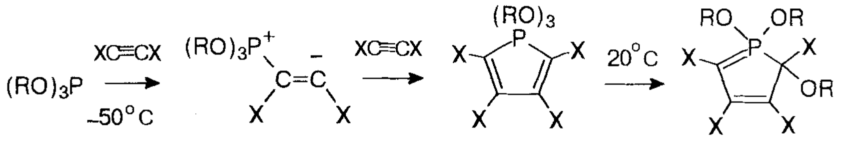


12 **13**

(5.7)

b) Reaction with Alkynes

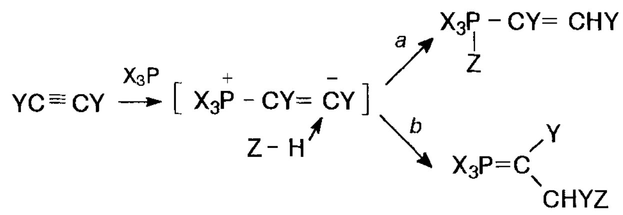
The reaction of tervalent phosphorus compounds with acetylenedicarboxylic acid esters results in phosphorus ylides. Tebby et al.[30] and Burgada et al.[31] found that the reaction of methyl acetylenedicarboxylate with trialkylphosphites leads to the formation of cyclic ylides containing alkoxy groups on the phosphorus atom. Low-temperature NMR study of the reaction showed that a betaine is formed initially and its reaction with a second acetylenedicarboxylate molecule gives rise to phosphorane **15**. At room temperature phosphoranes **15** are converted into cyclic ylides **16** which were isolated as crystalline products (Eq.5.8)[30,31]:



14 **15** **16**

(5.8)

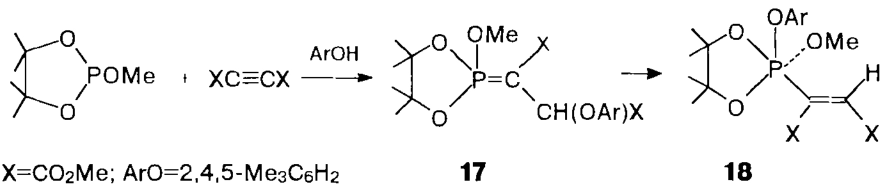
In the presence of hydroxylated reagents (methanol, phenol, benzoic acid, phthalimide), the reaction of acetylenedicarboxylates with phosphites leads to the formation of ylides or phosphoranes (Scheme 5.4):.



Scheme 5.4

Detailed studies have shown that the reaction proceeds via the formation of betaine, which is protonated by reagent ZH with the formation of phosphorane (route a), or ylide (route b), depending on the nature of substituents X and Y [32-34]. Acyclic phosphites give rise to ylides, whereas five-membered cyclic phosphites yield the phosphoranes.[35-37]

Interesting transitions between the ylide and phosphorane structures, the direction of which depends on the substituent R on the phosphorus atom and on the nature of the proton-donating reagent, have been observed by ^{31}P NMR. The reaction of 2,4,6-trimethylphenol with a cyclic phosphite and methyl acetylenedicarboxylate results in a ylide which is stable at room temperature and which on heating to 160°C rearranges into vinylphosphorane **17** (Eq.5. 9)[33]. The reaction of cyclic phosphites with methyl acetylenedicarboxylates and acetylacetone leads quantitatively to the formation of ylides **18**[34].

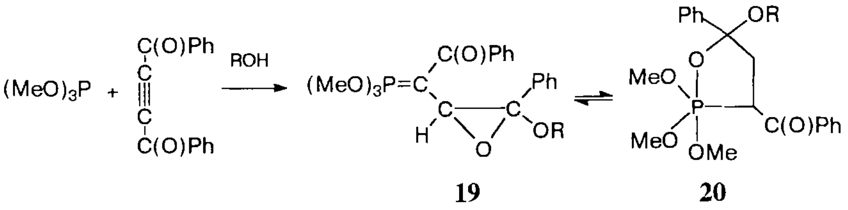


(5.9)

Trimethoxyphosphonium 2-methoxy-1,2-bis(methoxycarbonyl)ethylide (**17**, R = MeO, X = CO_2Me, R = Me)

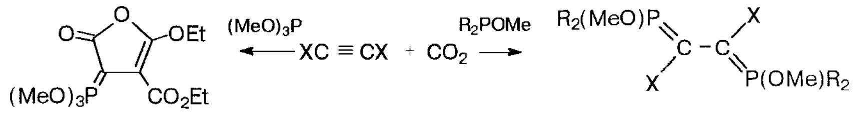
A solution of methyl acetylenedicarboxylate (1.42 g, 0.01 mol) in dichloromethane (10 mL) and methanol (5 mL; excess) was added dropwise at –50°C with stirring under dry nitrogen to a solution of trimethylphosphite (1.24 g, 0.1 mol) in dichloromethane (10 mL). The mixture became yellow. The course of the reaction was monitored by ^{31}P NMR. The temperature of reaction mixture was raised to 20°C and the residue was distilled under vacuum to furnish the product in 82% yield, bp 148°C (1.3 HPa).

Reaction of the trimethylphosphite with methanol or with phenol and dibenzoylacetylene furnishes ylide **19** bearing an epoxy group which exists in tautomeric equilibrium with the five-membered cyclic phosphorane **20** (Eq.5.11)[35,36]:



(5.10)

The reaction of phosphoric acid esters with methyl acetylenedicarboxylate in the presence of carbon dioxide proceeds with the formation of ylides **13**. Trialkylphosphites afford cyclic ylides **21**[37] whereas with methyl diphenylphosphonite bis-ylides **22** were obtained (Eq.5.11)[39,40]:



21 **22** (5.11)

X=CO$_2$Me

5.1.1.3 Synthesis from Phosphonium Salts

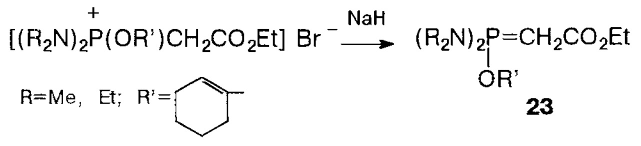
The salt method is used comparatively rarely for preparation of P–O ylides. Thus the treatment of methyl-tris(phenoxy)phosphonium iodide with the sodium hydride in THF leads to the formation of the tris-phenoxyphosphonium methylide which without isolation from the reaction mixture was used as the ligand for the preparation of transition metal complexes (Eq.5.12)[41]:

$$(PhO)_3P \xrightarrow{MeI} [(PhO)_3PMe]I^- \xrightarrow[NaI^-]{NaH} (PhO)_3P{=}CH_2 \qquad (5.12)$$

Triphenoxyphosphonium methylide[41]

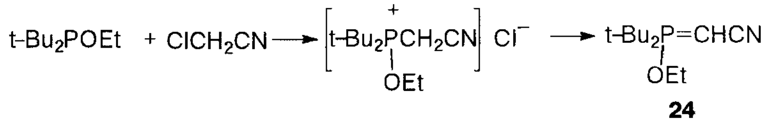
Methyltriphenoxyphosphonium iodide (4.88 mmol), THF (70 mL), and a suspension of sodium hydride (80%; 0.35 g, 11 mmol) were placed in a 250-mL flask, heated under argon to 50–60°C for 1 h with stirring, and then left overnight at room temperature. The salt precipitate was separated, the solution was evaporated to 40 mL, and the prepared solution of ylide was used for further transformations without isolation.

The «salt method» is rarely used for the synthesis of ylides with alkoxy groups on the phosphorus atom because of the instability of alkoxyphosphonium salts. The formation of ylides **23** proved to be possible because of the unique stability of vinyloxyphosphonium salts (Eq.5.13)[42]. The reaction of ethyl di-*tert*-butylphosphinite with chloroacetonitrile also affords ylide **24** in low yield (Eq.5.14)[43]:



$$[(R_2N)_2\overset{+}{P}(OR')CH_2CO_2Et]\,Br^- \xrightarrow{NaH} (R_2N)_2\underset{\displaystyle OR'}{P}{=}CH_2CO_2Et \qquad (5.13)$$

23



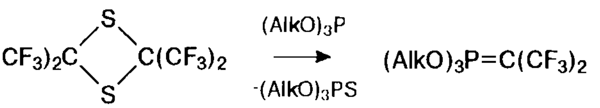
$$t\text{-}Bu_2POEt + ClCH_2CN \longrightarrow \left[t\text{-}Bu_2\underset{\displaystyle OEt}{\overset{+}{P}}CH_2CN\right] Cl^- \longrightarrow t\text{-}Bu_2\underset{\displaystyle OEt}{P}{=}CHCN \qquad (5.14)$$

24

5.1.1.4 Reaction of Trialkylphosphites with Carbenes

Methods have been reported for the synthesis of trialkoxyphosphonium ylides by reaction of trialkylphosphites with carbenes. One of the first examples of such syntheses was the reaction described by Midlleton. The reaction of trialkylphosphites with hexafluorothioacetone led to the formation of trialkoxyphosphonium hexafluoroisopropylides **25** (Eq.5.15)[44]. The formation of a carbene intermediate, which then reacts with the second phosphite molecule, has been postulated. Trialkylphosphites reacted analogously with the hexafluoroacetone dimer (Eq.5.16). Ylides **25** are stable, vacuum-distillable liquids.

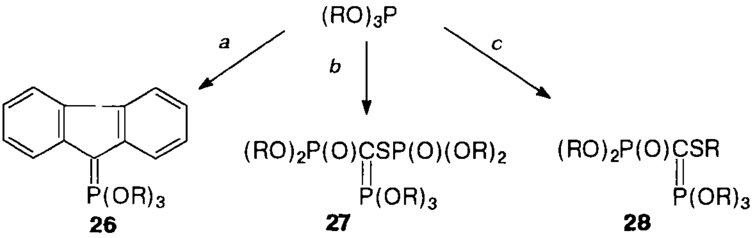
$$(CF_3)_2C{=}S \xrightarrow[-(RO)_3PS]{(RO)_3P} (CF_3)_2C: \xrightarrow{(RO)_3P} (RO)_3P{=}C(CF_3)_2 \qquad (5.15)$$



(5.16)

Trimethoxyphosphonium bis(trifluoromethyl)methylide **25** (Eq.5.16)[44]
Hexafluoroacetone dimer (12.1 g, 0.033 mol) was added dropwise with stirring to trimethylphosphite (24.8 g, 0.2 mol), with cooling in an ice-bath. During addition of hexafluoro-acetone the temperature of the reaction mixture increased to 30°C. The reaction mixture was fractionated under reduced pressure. Yield 14.4 g, bp 61–62°C (0.35 mm Hg), n_D 1.3664.

Reaction of fluorenthione with trimethylphosphite results in the formation of fluorenylide **26**, a colorless, stable, crystalline compound (Scheme 5.5)[45]:



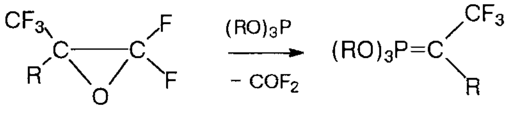
R=Alk, *a*=9-Fluorenethion,[45] *b*=MeSC(S)CCl$_3$, or CSCl$_2$ [45] *c*=(RO)$_2$P(O)C(S)SR$_2$ [50]

Scheme 5.5

Trialkylphosphites react with methyl trichlorodithioacetic acid, and with thiophosgene with the formation of trialkoxyphosphonium ylides **27**, **28** with a phosphono or phosphoryl group on the ylidic carbon atom (Scheme 5.5)[46].

Other examples have been found of the synthesis of trialkoxyphosphonium ylides by reaction of trialkylphosphites with thioketones[47]. The reaction of trialkylphosphites

Other examples have been found of the synthesis of trialkoxyphosphonium ylides by reaction of trialkylphosphites with thioketones[47]. The reaction of trialkylphosphites with esters phosphonoformic acids proceeds analogously[50]. It has been shown that epoxy derivatives of perfluorinated alkenes react with trialkyl phosphites to give ylides **29** (Eq.5.17)[48,49]:

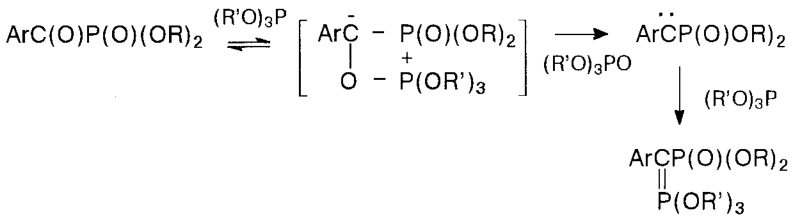


(5.17)

29

R= CF_3, CO_2R,[48] C_6F_5[49]

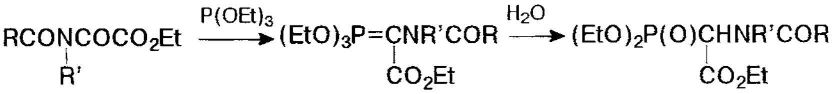
The formation of the trimethoxyphosphonium ylide by reaction of tri(phenylthio)methyllithium with trimethylphosphite has been reported. Griffits and Tebby[51] reported a convenient method for the synthesis of trialkoxyphosphonium ylides by reaction of trialkylphosphites with aroylphosphonates. It was found that the reaction proceeds with the formation of anionic intermediates which in the absence of electrophiles are converted into carbenes by heating to 80°C. Then carbenes undergo intramolecular reaction with excess trialkylphosphites to afford trialkylphosphonium ylides **30** in almost quantitative yield (Scheme 5.6)[51a,b]:



30

Scheme 5.6

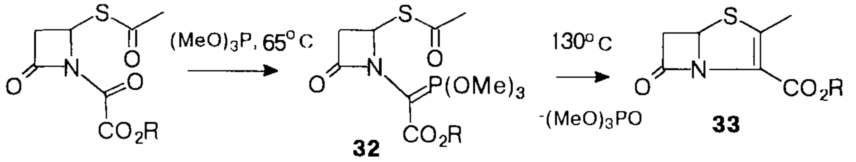
Seki and Matsumoto obtained trialkylphosphonium ylides by reaction of trialkylphosphites with acyl amides (Eq.5.18)[52,53]:



$$\mathrm{RCO}\underset{R'}{\mathrm{N}}\mathrm{COCO_2Et} \xrightarrow{P(OEt)_3} \mathrm{(EtO)_3P{=}}\underset{CO_2Et}{\mathrm{C}}\mathrm{NR'COR} \xrightarrow{H_2O} \mathrm{(EtO)_2P(O)}\underset{CO_2Et}{\mathrm{C}}\mathrm{HNR'COR} \qquad (5.18)$$

31

This method is of important practical application for the synthesis of *β*-lactam antibiotics, in particular, derivatives of penem and cephem acids which are structural hybrids of penicillin and cephalosporin (Eq.5. 19)[54a–c].

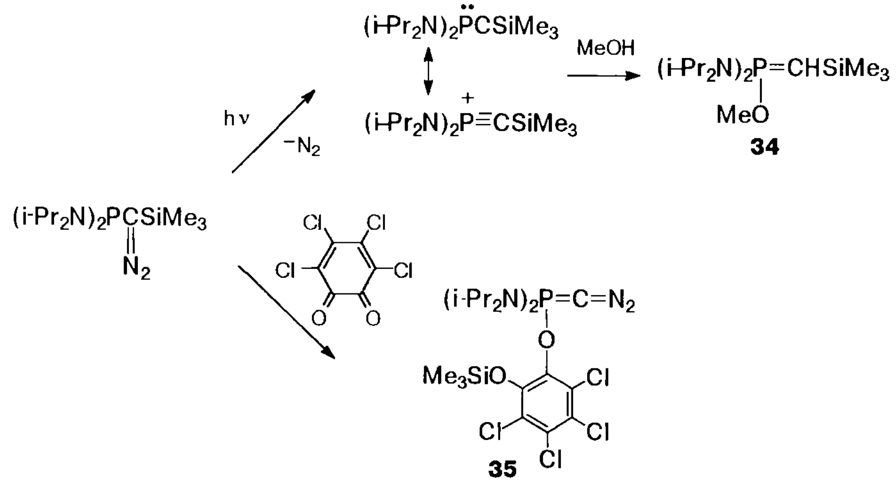


(5.19)

The reaction of a trialkylphosphite with appropriate carbonyl compounds proceeds with gentle heating resulting in trialkoxyphosphonium ylides **32**, which then under reflux in xylene undergo intramolecular cyclization to produce β-lactam derivatives **33**.
Reviews of examples of syntheses show that the reaction of trialkylphosphites with compounds capable of generating carbenes is one of the important methods for the preparation of alkoxyphosphonium ylides.

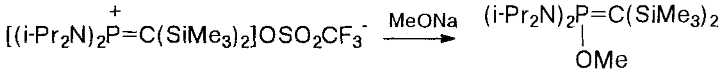
5.1.1.5 Other Methods of Preparation

Interesting methods have been reported for the synthesis of alkoxyphosphonium ylides but have found limited application. Baceiredo and Bertrand obtained alkoxyphosphonium ylide **34** by photolysis of bis(diisopropylamino)phosphine (trimethylsilyl)diazomethane in the presence of methanol. The reaction proceeded via the formation of phosphinecarbene (Scheme 5.7)[55]. The phosphine(trimethylsilyl) diazomethane reacted with *ortho*-quinones to afford P–O ylides **35**[56]:



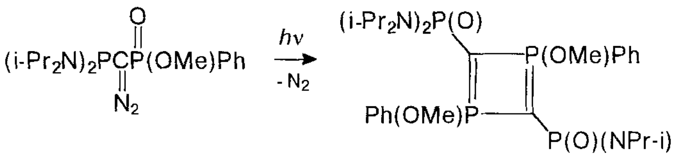
Scheme 5.7

In other work the same authors found that in the presence of a crown ether the phosphonium cation added sodium methylate with the formation of bis(diisopropylamino)methoxyphosphonium bis(trimethylsilyl)methylide (Eq.5.20)[57]:



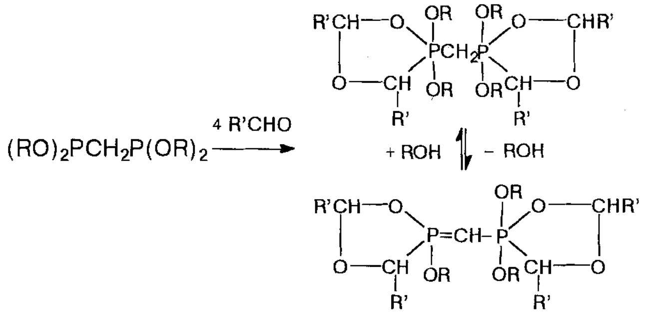
$$[(i\text{-}Pr_2N)_2\overset{+}{P}{=}C(SiMe_3)_2]OSO_2CF_3^- \xrightarrow{MeONa} (i\text{-}Pr_2N)_2\underset{\displaystyle OMe}{\underset{|}{P}}{=}C(SiMe_3)_2 \tag{5.20}$$

Regitz and coworkers[58] reported that the photolysis of phospinephosphonium diazomethane resulted in a four-membered cyclic diphosphetane. The formation of this compound probably proceeds via a carbene intermediate (Eq.5.21):



(5.21)

The reaction of tetraalkyl[methylene-bis(phosphonites)] with aliphatic aldehydes proceeds with a 1:1–1:4 ratio of starting reagents at room temperature to result in the formation of methyl [bis(2,2-dialkoxy-1,4,2-dioxaphospholanes)] which readily eliminate a molecule of alcohol to form ylides (Scheme 5.8)[59]:



Scheme 5.7

5.1.2 Properties

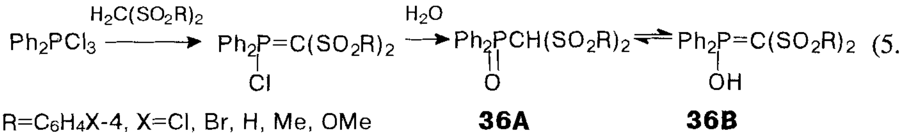
5.1.2.1 Phosphine Oxide–Ylide Tautomerism

Some reactions and chemical properties of phosphoryl compounds are similar to the properties of carbonyl compounds. Thus CH phosphine oxide–POH ylidic tautomerism, shown for diphenyl bis (phenylsulfonyl) methylphosphinoxide in the example (Eq.5.22), is analogous to keto–enol tautomerism[60,61].

$$\underset{\displaystyle O}{\underset{\|}{R_2P}}CHR'_2 \rightleftharpoons \underset{\displaystyle HO}{\underset{|}{R_2P}}{=}CR'_2 \tag{5.22}$$

C **D**

The tautomeric equilibrium (**C**) $\rightleftharpoons$ (**D**) is displaced towards the OH form (**D**) for diphenyl-bis(arenesulfonyl)methylphosphine oxides, which contain substituents with strong electron-accepting properties. In the crystalline state these phosphine oxides occur as the pure CH phosphine oxide whereas in solution they are present as a tautomeric mixture of the OH ylide **36A** and the CH phosphine oxide **36B.** The OH and CH forms can be readily detected by spectroscopic methods (IR, and ^{1}H and ^{31}P NMR) (Eq.5.23, Table 5.2):



$$\mathrm{Ph_2PCl_3} \xrightarrow{\mathrm{H_2C(SO_2R)_2}} \mathrm{Ph_2\underset{\displaystyle Cl}{\underset{|}{P}}{=}C(SO_2R)_2} \xrightarrow{\mathrm{H_2O}} \mathrm{Ph_2\underset{\displaystyle O}{\underset{\|}{P}}CH(SO_2R)_2} \rightleftharpoons \mathrm{Ph_2\underset{\displaystyle OH}{\underset{|}{P}}{=}C(SO_2R)_2} \quad (5.23)$$

R=C$_6$H$_4$X-4, X=Cl, Br, H, Me, OMe **36A** **36B**

Diphenyl-bis(phenylsulfonyl)methylphosphine oxide (**36A** $\rightleftharpoons$ **36B**, X = H)[61,62]

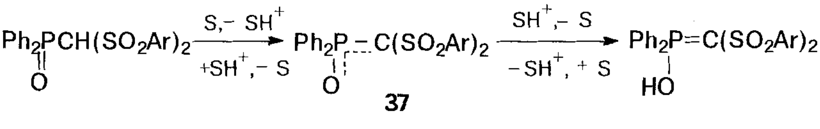
(a) *Chloro(diphenyl)phosphonium bis(phenylsulfonyl)methylide*

A two-necked, round-bottomed flask was equipped with a magnetic stirrer, a reflux condenser, and a pressure-equalizing dropping funnel fitted with a drying tube. A solution of diphenyltrichlorophosphorane (28.85 g, 0.1 mol) in anhydrous THF (100 mL) was placed in the flask and a solution of bis(phenylsulfonyl)methane (29.64 g, 0.1 mol) and triethylamine (20.88 mL, 0.15 mol) in THF (100 mL) was added dropwise with stirring at 0°C. When addition was complete the stirred mixture was left to warm to room temperature, was stirred for another 15 min, and subsequently heated under reflux for 15 min. The precipitate of Et$_3$N.HCl was removed by filtration, the solvent was evaporated under reduced pressure, and the residue was recrystallized from benzene. The yield of chloro(diphenyl)phosphonium bis(phenylsulfonyl) ethylide was 35.98 g (70%), mp 191°C. ^{31}P NMR spectrum, δ_P 55 ppm.

(b) *Diphenyl-bis(phenylsulfonyl)methylphosphine oxide*

Chloro(diphenyl)phosphonium bis(phenylsulfonyl)methylide (25.70 g, 0.05 mol) was dissolved in acetone (100–150 mL) in a 250-mL round-bottomed flask and water (10 mL) was added to the solution and the reaction mixture was left to stand for 12 h at room temperature. After evaporation of the solvent under reduced pressure, the residue was recrystallized from benzene. Yield 23.59 g (95%), mp 209°C.

The tautomeric equilibrium (**C**) $\rightleftharpoons$ (**D**) is mobile and depends on the temperature, and the nature of solvents and substituents. The amount of the ylide form increases with decreasing temperature and this form is evidently energetically more favorable. Electron-accepting substituents in the *para* positions of the arenesulfonyl groups increase the amount of the ylide form, because they enhance the delocalization of the negative charge of the ylide carbon atom. (Table 5.2). Study of the prototropic equilibrium in aqueous alcoholic solutions showed a two-stage mechanism of tautomeric transformation; the anion **37** formed in these solvents had a strong tendency to dissociate (Eq 24):



$$\mathrm{Ph_2\underset{\displaystyle O}{\underset{\|}{P}}CH(SO_2Ar)_2} \underset{\mathrm{+SH^+,-\,S}}{\xrightarrow{\mathrm{S,-\,SH^+}}} \mathrm{Ph_2\underset{\displaystyle O}{\underset{\vdots}{P}}\cdots C(SO_2Ar)_2} \underset{\mathrm{-SH^+,+\,S}}{\xrightarrow{\mathrm{SH^+,-\,S}}} \mathrm{Ph_2\underset{\displaystyle HO}{\underset{|}{P}}{=}C(SO_2Ar)_2} \quad (5.24)$$

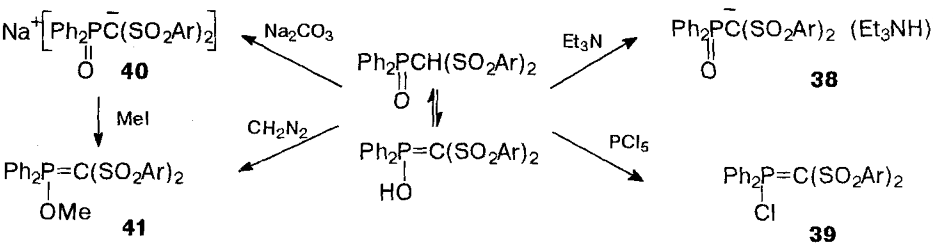
37

Table 5.2. The tautomeric composition of diphenyl-bis(benzenesulfonyl) methylphosphine oxides **36A** ⇌ **36B** (Eq.23) [61]

X	**36A** (%)	**36B** (%)	K_T	Solvent	Temp °C	pK_a*
Cl	43	57	1.32	THF	20	3.55
	48	52	1.08	THF	30	-
	51	49	0.96	THF	40	-
	53	47	0.86	THF	55	-
	80	20	0.25	CCl_4	25	-
	86	16	0.16	$CHCl_3$	25	-
	90	10	0.11	CH_2Cl_2	25	-
H	80	20	0.25	THF	25	3.60
	96.5	35	0.036	$CHCl_3$	25	-
Me	90	10	0.11	THF	25	3.62
MeO	90-98	2-4	-	THF	25	3.68

*) in 50% methanol

Diphenyl bis(arenesulfonyl)methylphosphine oxides have interesting properties, resembling those of the OH acids of tetracoordinate phosphorus. These extremely stable compounds are comparatively strong acids (pH 3.55–3.68 in 50% alcohol) (Scheme 5.9). They readily dissolve in aqueous sodium carbonate, from which they can be recovered quantitatively by acidifying the solution. They react with triethylamine to form stable triethylammonium salts **38**. Reaction of the compounds with phosphorus pentachloride gives rise to the P-chloro derivatives **39**. The reaction of phosphine oxide with diazomethane leads to the formation of an O-methylated product, ylide **41**. This product was also prepared by reaction of the sodium salt **40** with methyl iodide.

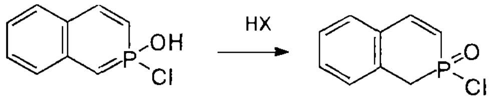


Scheme 5.8

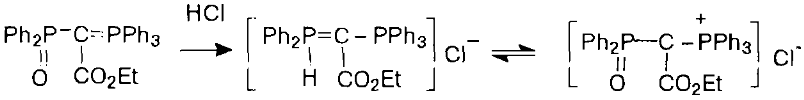
Methoxy diphenyl phosphonium-bis(phenylsulfonyl)methylide **41** (Scheme 5.9)[61,63]

A solution of diphenyl bis(phenylsulfonyl)methylphosphine oxide (0.01 mol) in THF (50 mL) was added to a cooled (0°C) solution of diazomethane (0.012 mol) in ether. The reaction solution was stirred for 15–20 min at 20°C and then gradually warmed to room temperature over a period 30–45 min, The reaction mixture was evaporated to dryness and the residue was recrystallized from benzene–hexane (~1:1). Yield 75%, mp 191°C.

Phosphine oxide–ylide tautomerism was first discovered for, and investigated on, diphenyl bis(arenesulfonyl)methylphosphine oxide **36**, X = H[61,63]. Subsequently other OH ylides were also described. Cyclic P-oxy-1-phosphorin, which is stable in the crystalline state and which rearranges irreversibly to the more stable isomer with a P=O group in the presence of proton-donating reagents, has been synthesized (Eq.5.25)[64]. Mastrukova and Kabachnik observed the formation of oxidylide forms by protonating phosphorus substituted phosphorane-phosphonium salts (Eq.5.26)[65,66]:



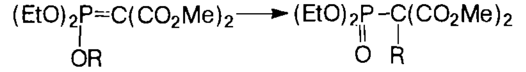
(5.25)



$$\underset{\substack{\| \\ O}}{Ph_2P}-\underset{\substack{| \\ CO_2Et}}{C}=PPh_3 \xrightarrow{HCl} \left[Ph_2P=\underset{\substack{| \\ H}}{}\underset{\substack{| \\ CO_2Et}}{C}-PPh_3\right]Cl^- \rightleftharpoons \left[Ph_2\underset{\substack{\| \\ O}}{P}-\underset{\substack{| \\ CO_2Et}}{C}-\overset{+}{P}Ph_3\right]Cl^- \qquad (5.26)$$

5.1.2.2 Phosphorus Ylide-Phosphonate Rearrangement

The ylides containing alkoxy groups on the phosphorus atom are readily dealkylated to form phosphonates. Thus alkoxyphosphonium ylides **44** rearrange on heating to phosphonates with migration of an alkyl group to the ylide carbon atom (the ylide version of the Pishchimuka reaction) (Eq.5.27):

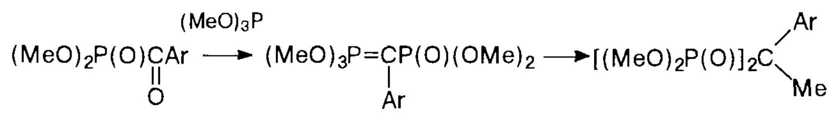


$$(EtO)_2\underset{\substack{| \\ OR}}{P}=C(CO_2Me)_2 \longrightarrow (EtO)_2\underset{\substack{\| \\ O}}{P}-\underset{\substack{| \\ R}}{C}(CO_2Me)_2 \qquad (5.27)$$

R=Me, Et, i=Pr

The rearrangement of ylides with a methoxy group is complete after several days at 20°C, but at 80–100°C ylides are rapidly transformed into the phosphonate[6]. Ylides with ethoxy or isopropoxy groups on the phosphorus atom are more stable than the corresponding ylides with methoxy groups. They are converted into phosphonates only on heating to 150–180°C.

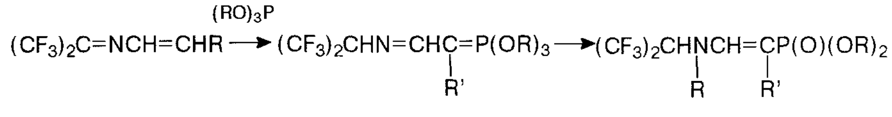
Ylide–phosphonate rearrangement often proceeds very easily. For instance, during their preparation ylides **42** rearrange quantitatively into diphosphonates **43** (Eq.5.28)[51]:



$$(MeO)_2P(O)\underset{\substack{\| \\ O}}{C}Ar \xrightarrow{(MeO)_3P} (MeO)_3P=\underset{\substack{| \\ Ar}}{C}P(O)(OMe)_2 \longrightarrow [(MeO)_2P(O)]_2C{\begin{smallmatrix} Ar \\ Me \end{smallmatrix}} \qquad (5.28)$$

42 **43**

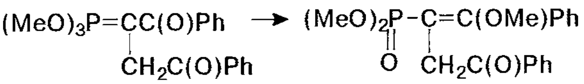
During ylide–phosphonate rearrangement the alkyl group can migrate not only to the α carbon, but also to other nucleophilic centers in the molecule. Ylides **44** with an imino group on the ylidic carbon atom, rearrange into phosphonates as a result of migration of the alkyl group to the nitrogen atom (Eq.5.29)[67]:



$$(CF_3)_2C{=}NCH{=}CHR \xrightarrow{(RO)_3P} (CF_3)_2CHN{=}CH\underset{R'}{C}{=}P(OR)_3 \longrightarrow (CF_3)_2CH\underset{R}{N}CH{=}\underset{R'}{C}P(O)(OR)_2 \qquad (5.29)$$

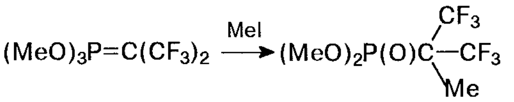
R=Me, Et **44**

Methoxyphosphonium ylides bearing phenacyl groups on the α carbon are converted into vinylphosphonates at room temperature as a result of the shift of the methyl group to the oxygen atom (Eq.5.30)[26]:



$$(MeO)_3P{=}\underset{CH_2C(O)Ph}{C}C(O)Ph \longrightarrow (MeO)_2\underset{O}{\overset{}{\underset{\|}{P}}}{-}\underset{CH_2C(O)Ph}{C}{=}C(OMe)Ph \qquad (5.30)$$

Electron-accepting substituents, which reduce the nucleophilicity of the ylide carbon atom, hinder the rearrangement. Thus ylides containing the powerful electron-accepting benzenesulfonyl groups on the α carbon atom are stable and do not change on heating to 200°C[6]. Alkyl halides catalyze ylide–phosphonate rearrangement. For instance, rearrangement of trimethoxyphosphonium hexafluoroisopropylide into the phosphonate normally proceeds on heating to 180°C but in the presence of methyl iodide proceeds at a lower temperature (Eq.5. 31). The mechanism of the catalyzed rearrangement probably includes addition of methyl iodide to the P=C bond.[44,48]:

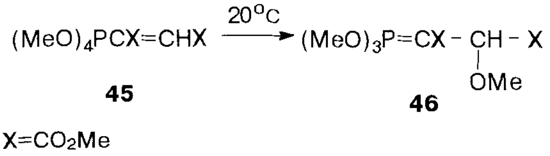


$$(MeO)_3P{=}C(CF_3)_2 \xrightarrow{MeI} (MeO)_2P(O)\overset{CF_3}{\underset{Me}{C}}{-}CF_3 \qquad (5.31)$$

5.1.2.3 Phosphorus Ylide–Phosphorane Transformation

There is significant interest in the tautomeric equilibrium between ylide and phosphorane structures. Ylide–phosphorane conversions the direction of which depends on substituents R on the phosphorus and on the nature of proton-donating reagent have been studied by ^{31}P NMR spectroscopy[34]. Rearrangement of ylide into phosphorane was studied during reaction of trimethylphosphite with acetylendicarboxylic acid ester in dichloromethane in the presence of methanol as trapping reagent. At 40°C phosphorane **45** was detected in the reaction mixture; at room temperature this was quantitatively converted into the ylide **46** (Eq.5.32):

In the course of the ylide–phosphorane tautomeric equilibrium the R group migrates between the phosphorus and carbon atoms in the P–C–C triad, resulting in variation of the coordination of the phosphorus atom. The position of the tautomeric equilibrium

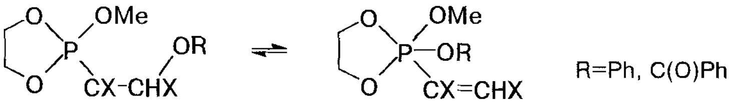


$$(MeO)_4PCX{=}CHX \xrightarrow{20^oC} (MeO)_3P{=}CX-\underset{OMe}{\underset{|}{C}}H-X \qquad (5.32)$$

45 **46**

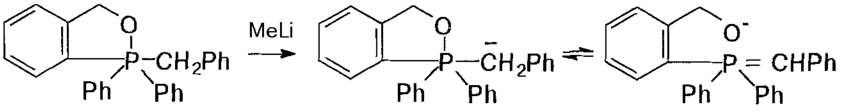
X=CO2Me

depends on the solvent and on the substituent R. When R = Ph the tautomeric equilibrium is shifted towards the phosphorane; when R = C(O)Ph both tautomeric forms are present in the solution and can be detected by NMR. The dependence of the position of the tautomeric equilibrium on the nature of the solvent is such that **47** : **48** = 18:82 in CCl_4 and 37:63 in CH_2Cl_2 (Eq.5.33)[34]:



47 **48** (5.33)

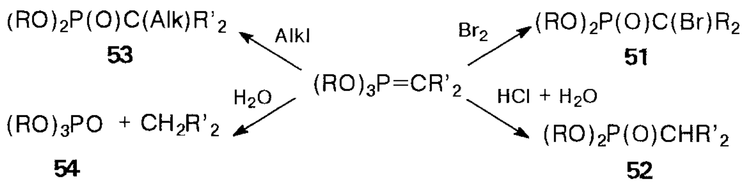
Another example of the ylide–phosphorane tautomeric equilibrium was found in the metallation of the phosphorane **49** with benzylic group on the phosphorus. Treatment of phosphorane **49** with methyllithium leads to the formation of oxaphosphorane carbanion **50A** in tautomeric equilibrium with ylide **50B**[69]. The tautomeric equilibrium **50A** $\rightleftharpoons$ **50B** depends on the temperature (Eq.5.34):



49 **50A** **50B** (5.34)

5.1.2.4 Miscellaneous

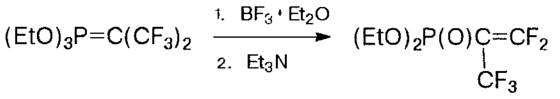
Alkoxyphosphonium ylides are dealkylated on interaction with hydrogen chloride, bromine, and alkyl halides[6]. Alkoxyphosphonium ylides react with bromine to afford bromophosphonates **51** and reaction with dilute hydrochloric acid furnishes phosphonates **52**[48]. Hydrolysis of ylides containing alkoxy groups o the phosphorus atom proceeds both with elimination of one of the alkyl groups and cleavage of the P=C bond to afford alkylphosphates **54** (major product) and phosphonates **52** (Scheme 5.10)[44,70]:



R=Me, Et; CR'_2= $C(CF_3)_2$, $C(CO_2Me)_2$, $C[CH_2C(O)Ph]C(O)Ph$

Scheme 5.10

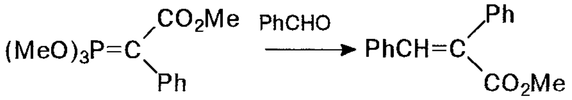
When the ylide was treated with boron trifluoride etherate, the phosphorus analog of the perfluoromethacrylic ester 55 was obtained as a result of simultaneous dealkylation and elimination of a fluorine atom (Eq.5.35)[44]:



$$(EtO)_3P{=}C(CF_3)_2 \xrightarrow[2.\ Et_3N]{1.\ BF_3 \cdot Et_2O} (EtO)_2P(O)C(CF_3){=}CF_2 \qquad (5.35)$$

55

Alkoxyphosphonium ylides normally undergo the Wittig reaction and their reactivity is probably comparable with those of triphenylphosphonium ylides (Eq.5.36)[17,71]:



$$(MeO)_3P{=}C(CO_2Me)Ph \xrightarrow{PhCHO} PhCH{=}C(Ph)CO_2Me \qquad (5.36)$$

Application of P–OAlk ylides in the synthesis of juvenile hormones analogs has been reported[70b].

In conclusion, alkoxyphosphonium ylides are thermally less stable than triphenylphosphonium ylides. They have high alkylating capacity and are readily dealkylated to furnish phosphonates

5.2 P–N Ylides

Ylides of phosphorus containing a P–N bond in the phosphorus atom (P–N ylides), and the triphenylphosphonium ylides, are valuable reagents for the olefination of carbonyl compounds and for the Wittig reaction. P–N ylides also some specific features. Firstly they are stronger nucleophiles than P–C ylides, because of the electron-donating influence of the amino groups. Ylides with dialkylamino groups on the phosphorus atom are available and are very reactive; this has attracted much interest to these compounds. The reactivity and stability of dialkylaminophosphonium ylides depend on the substituents on the ylide carbon atom. Dialkylaminophosphonium ylides stabilized by electron-accepting substituents are indeed very stable. In general, P–N ylides are more stable to hydrolysis than are triphenylphosphonium ylides.

5.2.1. Synthesis

P–N ylides can be obtained by methods developed for the preparation of triphenylphosphonium ylides. Important synthetic methods are the salt method and the reaction of trivalent phosphorus compounds with alkenes and alkynes.

5.2.1.1 Syntheses from Phosphonium Salts

The simplest method for the preparation of P–N ylides is the «salt method» and this is widely used for their preparation[72–80]. Accessible dialkylaminophosphonium salts are readily dehydrohalogenated by various bases, potassium and sodium hydrides, lithium amide, butyllithium, and sometimes by sodium ethylate or by aqueous solutions of alkalis (Table 5.3). Schmidbaur synthesized dialkylaminophosphonium ylides **56** by treatment of the appropriate phosphonium salt with potassium hydride (Eq.5.37).[72] C-silyl-substituted P–N ylides **57** were prepared analogously in high yields. The ylides were obtained as colorless stable, vacuum-distillable liquids (Eq.5.38)[80]:

$$(Et_2N)_{3-n}PMe_{n+1} + KH \longrightarrow \underset{\mathbf{56}}{(Et_2N)_{3-n}(Me)_nP{=}CH_2} \qquad (5.37)$$

$$(R_2N)_n(Me_{3-n})PCH_2SiMe_3]Cl + KH \rightarrow \underset{\mathbf{57}}{(R_2N)_n(Me_{3-n})P{=}CHSiMe_3} \qquad (5.38)$$

R=Me, Et; n=2,3

Table 5.3. Tris(dialkylamino)phosphonium methylides $(R_2N)_nR'_{3-n}P{=}CH_2$

R	R'	n	B	bp/p mmHg	Yield (%)	Ref
Me	Me	2	$NaNH_2$	66-67/15	72	73
Me	Me	1	$NaNH_2$	54-55/15	53	73
Me	-	3	$NaNH_2$	87-88/14	73	73
Et	Me	2	KH	53/1	60	101
Et	Me	1	KH	90/1	79	101
Et	Me	0	KH	83/0.1	82	101

Tris(diethylamino)phosphonium methylide (Eq.5.37)[72]

Methyl tris(diethylamino)phosphonium iodide (50 mmol, 19.47 g) was suspended in tetrahydrofuran (150 mL) and mixed with potassium hydride (55 mmol, 2.21 g). Gaseous hydrogen is evolved. The reaction mixture was heated under reflux for 10 h and then filtered. The filtrate was evaporated and the residue was distilled under vacuum. Yield 10.74 g (82%), bp 83°C (0.1 mm Hg).

Issleib and coworkers synthesized non-stabilized ylides by treating a phosphonium salt with sodium amide in liquid ammonia (Eq.5.39)[73,74]. Ylides **58** were colorless stable, vacuum-distillable liquids.

$$[(Me_2N)_n(Me)_{4-n}\overset{+}{P}]\ Br^- \xrightarrow[-NaBr]{NaNH_2/NH_3} (Me_2N)_n(Me)_{3-n}P{=}CH_2 \qquad (5.39)$$

$n=1\text{-}3$ **58**

Tris(dimethylamino)phosphonium methylide (Eq.5.39, $n = 3$)
Methyl-tris(dimethylamino)phosphonium bromide (8.5 g, 0.025 mol) and toluene (100 mL) were placed in a 200-mL round-bottomed flask and solid sodium amide (0.025 mol) was added slowly with stirring. The mixture was stirred for 24 h at 85–100°C, cooled to room temperature and centrifuged to separate sodium bromide. The filtrate was concentrated under reduced pressure and the residue was distilled in vacuum to provide the desired product as a colorless liquid. Yield 25 g (65%), bp 90–94°C (15 mm Hg).

Benzylides **59** were obtained by treatment of phosphonium salts with butyl lithium or with sodium ethylate (Eq.5.40)[75–78]:

$$[(R_2N)_3\overset{+}{P}CH_2Ph]\ Hal^- \xrightarrow{BuLi\ \text{or}\ EtONa} (R_2N)_3P{=}CHPh \qquad (5.40)$$

R=Me, Et **59**

Stable ylides bearing alkoxycarbonyl or dialkylaminocarbonyl groups on the phosphorus atom have been prepared by treatment of phosphonium salts with aqueous alkali—sodium ethylate or potassium *tert*-butoxide (Eq.5.41,42)[75,78]:

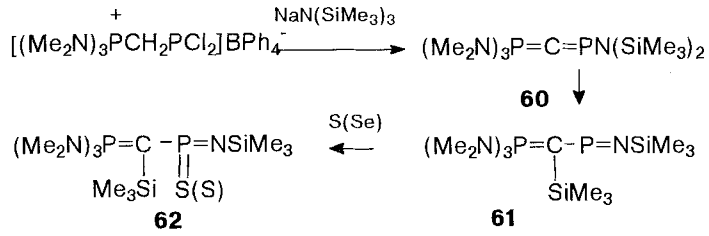
$$[(Me_2N)_2(R)\overset{+}{P}CH_2CO_2Et]Br^- \xrightarrow{B} (Me_2N)_2(R)P{=}CHCO_2Et \qquad (5.41)$$

$$[(R'_2N)_3\overset{+}{P}CH_2C(O)NEt_2]Cl^- \xrightarrow{B} (R'_2N)_3P{=}CHC(O)NEt_2 \qquad (5.42)$$

R=Me, Et; R'=Me_2N, Ph; B=NaOEt, NaOH/H_2, t-BuOK

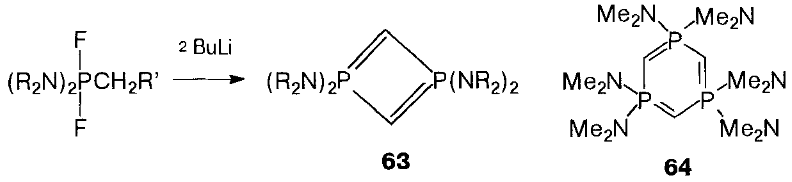
Wittig synthesized dialkylaminophosphonium ylides by treatment of phosphonium salts with butyllithium which were reacted with carbonyl compounds without isolation from solution. Ylides were obtained as complexes with lithium chloride[69].

Reaction of (dichlorophosphinyl)methylphosphonium salt with sodium bis (trimethylsilyl) amide in THF at –78°C affords the diphosphaallene **60**; this undergoes 1,3-silyl migration to produce phosphoryl-disubstituted iminophosphine **61** (Scheme 5.11). X-Ray crystallography showed that the compound can be described as an allylic anion with a four-electron three-centered C–P–N bond. The shortened P=C and Si–C bonds, 1.700(4) and 1.836(4) Å, respectively, are of particular interest. The oxidative addition of sulfur or selenium to **61** affords phosphoryl-disubstituted iminothioxo) hosphorane or imino (selenoxo)phosphorane **62**[83].



Scheme 5.11

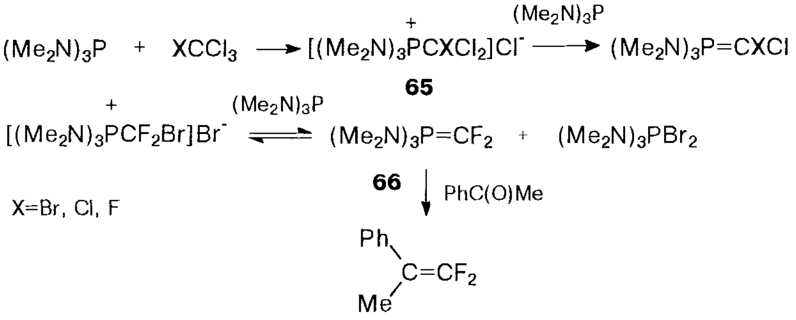
E.Fluck obtained four-membered cyclic bis-ylide-diphosphetanes **63** and six-membered cyclic tris-ylide-1,2.3,5-triphosphabenzene **64** by treatment of difluorophosphoranes with butyl lithium or *tert*-butyllithium (Scheme 5.12).[84-86]



Scheme 5.12

The structure of diphosphetanes **63** was confirmed by X-Ray crystallography which showed the planar structure of the cyclic fragment of the molecule with completely equal P–C bond-lengths[84]. The six-membered ring of triphosphetane **64** was also almost planar with equal distances between the atoms[86].

Dialkylaminophosphonium ylides bearing a dihalomethyl group are synthesized by dehalogenation of trihalomethylphosphonium salts **65** with triphenylphosphine or tris(dimethylamido) phosphite[88-92]. The reaction is usually performed without isolation of the phosphonium salts by treatment of the tetrahalomethane CX_4 = CCl_4, CBr_4, CCl_2F_2, CBr_2F_2, $CBrCl_3$ with excess tertiary phosphine. Highly reactive ylides can be generated by reaction of tris(dimethylamino)phosphine or triphenylphosphine with mixed fluorine-containing tetrahalomethanes or bromotrichloromethane in 2:1 ratio (Scheme 5.13)[93-95]. Barton showed that the reaction of tris(dimethylamido) hosphite with phosphonium salt affords ylides **44** which exist in equilibrium with the starting compounds, the equilibrium being shifted towards the phosphonium salt. In the presence of acetophenone the reaction leads to the formation of the olefin in 81% yield[88].

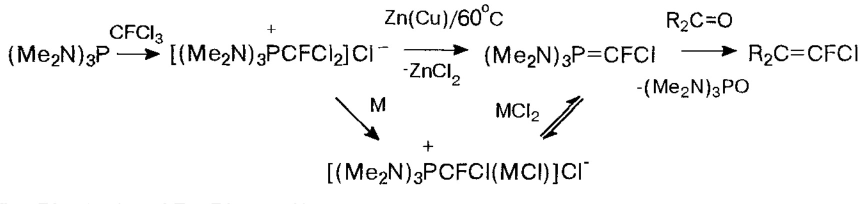


Scheme 5.13

Olefination of aldehydes with tris(dimethylamino)phosphonium dichloromethylide (Scheme 5.13)[95]

Bromotrichloromethane (39.66 g, 0.2 mol) was added to a solution of tris(dimethylamino) phosphine (81.61 g, 0.5 mol) in dichloromethane (100 mL) at –65°C. The reaction mixture was stirred for 30 min at –65°C and then the aldehyde in dichloromethane (50 mL) was added at this temperature. The temperature was increased to room temperature and the mixture was left overnight and then poured into icy water. The dichloromethane solution was separated, washed with aqueous hydrochloric acid (5%), then with water, and dried over magnesium sulfate. The solvent was evaporated and the residue was distilled under vacuum.

The reaction of tris(dimethylamino)phosphine with mixed fluorine-containing tetrahalomethanes furnishes phosphonium salts in high yields; dehalogenation of these leads to the formation of phosphorus ylides which are useful sources of difluoro-, chlorofluoro-, or bromofluoromethylene groups. Burton and Van-Hamme introduced the dehalogenation of phosphonium salts by reductive elimination with a Group II metal (zinc, cadmium, mercury); this can be considered to produce an organometallic phosphonium salt capable of undergoing the Wittig reaction with aldehydes and ketones. NMR spectroscopy showed that the reaction of a trihalomethylphosphonium salt with zinc gives a zinc–organic complex which dissociates to $ZnCl_2$ and the phosphorus ylide. In the stationary state the equilibrium is strongly shifted towards the salt, and the ylide cannot be detected by spectroscopic methods (Eq.5.43):



(5.43)

R =Ph, C_6H_{13}, CF_3; R'= H, Ph, CF_3, Me, AlkO, R=Ph, Me_2N.

In the presence of a carbonyl compound, however, the equilibrium is displaced towards the ylide, which can then undergo the Wittig reaction to form olefins in high yield. (Eq.5.43).[91]

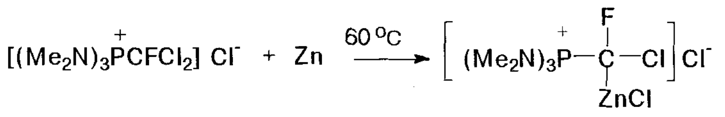
(Dichlorofluoromethyl)tris(dimethylamino)phosphonium chloride[91]

A solution of tris(dimethylamino)phosphine (44.3 g, 0.272 mol) in absolute diethyl ether (75 mL) was added dropwise over 2 h and with stirring at 0°C to a solution of trichlorofluoromethane (49.9 g, 0.363 mol) in absolute ether (350 mL). The reaction mixture was stirred for 2 h at 0°C, then left overnight at room temperature. The hygroscopic precipitate was removed by filtration under nitrogen, washed with ether, and dried under nitrogen to give 75.5 g (92%) of the complex salt.. Dec. 218°C.

E + Z-β-chloro-β-fluorostyrene

Zinc–copper couple (3.63 g, 10.9 mg-atom) was slowly added to benzaldehyde (1.04 g, 9.8 mmol) in THF (50 mL) under nitrogen with stirring at 45°C. The phosphonium salt was (3.94 g, 10.9 mmol) then added over a period of 10 min. The reaction mixture, which became dark brown, was heated for 1 h at 60°C. GC analysis showed the presence of a mixture of the *E* and *Z* isomers of chlorofluorostyrene. Yield 9.8 mmol (~100%).

In another example triphenylphosphine was reacted with trichlorofluoromethane in the presence of zinc powder at –60°C to result in a stable «quasi-complex» organometallic compound **67** which could be isolated. In solution this complex dissociates into the phosphorus ylide and zinc chloride and readily undergoes the Wittig reaction (Eq.5.44):



$$[(Me_2N)_3\overset{+}{P}CFCl_2]\,Cl^- + Zn \xrightarrow{60\,^{\circ}C} \left[(Me_2N)_3\overset{+}{P}-\underset{ZnCl}{\overset{F}{C}}-Cl\right]Cl^- \quad (5.44)$$

67

Chlorofluoro[tris(dimethylamino)(phosphoniummethyl]zinc)(II)chloride **67**[91]

Zinc–copper couple (1.68 and 27.8 mg, respectively), prepared from zinc dust (purity ~98%) by the LeGoff method, was stirred in tetrahydrofuran under nitrogen at a temperature below +40°C and (dichlorofluoromethyl)tris(diethylamino)phosphonium chloride (4.97 g, 16.5 mmol) was added over a period of 10 min keeping the temperature of the reaction solution below 60°C. The exothermic reaction resulted in a dark homogenous solution. The mixture was stirred for 15 min at 40–60°C and was then filtered to give the olefination reagent which is ready for use in syntheses.

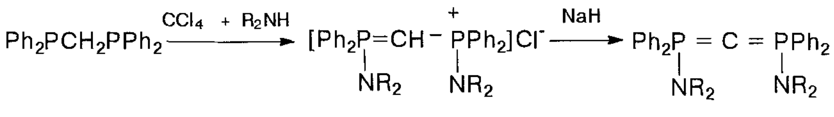
Tris(dialkylamino)phosphonium ylides and, especially, the stable complexes of these ylides with metals, have evident preparative advantages over triphenylphosphonium ylides as olefinating reagents and sources of the dihalomethylene group.

5.2.1.2 Oxidative Ylidation of Tertiary Amidoalkylphosphines

Tertiary amidoalkylphosphines with electron-accepting substituents on the α carbon atom are ylidated by reaction with carbon tetrachloride and alkylamines, aniline, or ammonia. This reaction is similar to the Atherton–Todd reaction, in which dialkyl phosphites react with CCl_4 and alkylamines to form phosphoric acid amides. Although the reaction with CCl_4 and alkylamines or ammonia proceeds readily in ether at 0°C, reaction with aniline must, because of its low basicity, be performed in the presence of triethylamine. The method employs readily available starting materials and enables wide variation of the substituents on the phosphorus and carbon atoms of the P=C group (Eq.5.45)[5,8–13]:

$$R^1_2PCHR^2_2 \xrightarrow[CHCl_3,\ -R^3_2NH\cdot HCl]{CCl_4\ /\ R^3_2NH} R^1_2P(NR^3_2){=}CR^2_2 \qquad (5.45)$$

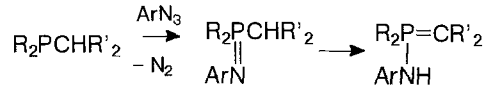
Appel and Waid reported a reaction of bis(diphenylphosphino)methane with carbon tetrachloride and dialkylamines in tetrahydrofuran at +20°C which resulted in the ylidephosphonium salt **68**. Dehydrochlorination of the latter with sodium hydride led to the formation of cumulene ylide **69** (Eq.5.46)[96]:



$$Ph_2PCH_2PPh_2 \xrightarrow{CCl_4\ +\ R_2NH} [Ph_2\underset{NR_2}{P}{=}CH^-\overset{+}{\underset{NR_2}{P}}Ph_2]Cl^- \xrightarrow{NaH} Ph_2\underset{NR_2}{P}=C=\underset{NR_2}{P}Ph_2 \qquad (5.46)$$

68 **69**

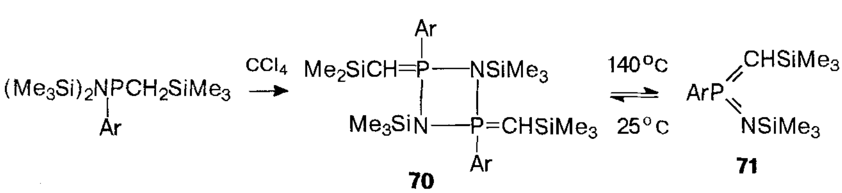
The use of tetravalent phosphorus compounds with a mobile hydrogen atom on the α carbon atom can be converted into ylides by reactions involving prototropic rearrangements. The Staudinger imination of bis(alkoxycarbonyl)methylphosphines and the analogous phosphonites by aryl azides yields the phosphazo compounds which readily rearrange to the ylides with the RNH group on the phosphorus atom. The driving force of this rearrangement is the endeavor by the system to form the least «acid» tautomer (Eq.5.47)[22]:



$$R_2PCHR'_2 \xrightarrow[-N_2]{ArN_3} R_2\underset{ArN}{\underset{\|}{P}}CHR'_2 \longrightarrow R_2\underset{ArNH}{P}{=}CR'_2 \qquad (5.47)$$

R=Alk, AlkO; $R'_2C{=}CPh_2$, $CHCO_2Me$, $C(Ph)CO_2Me$, $C(CO_2Et)_2$

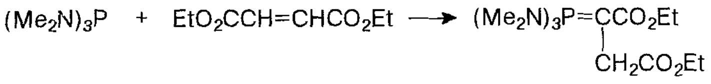
The reaction of alkyl(aryl)aminophosphines with the tetrahalomethane results in a four-membered cyclic ylide **70** which is a dimer of imino-methyl phosphorane. On heating to 140°C the ylide is converted into iminomethylenephosphorane **71**. At room temperature the iminomethylenephosphorane **71** again furnishes the cyclic ylide **70** (Eq.5.48)[97]:



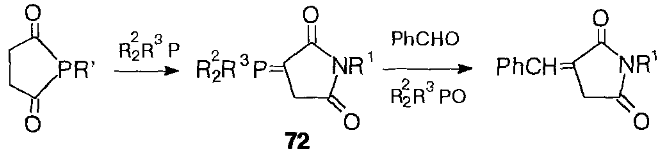
70 **71** (5.48)

5.2.1.3 Reaction of Tris(dialkylamino)phosphines with Alkenes and Alkynes

Derivatives of tervalent phosphorus readily add various maleimides and also of fumaric acid esters. Pudovik and coworkers obtained ylides 72 which react with benzaldehyde to afford appropriate olefins (Eq.5.49, Eq.5.50)[27-28]:



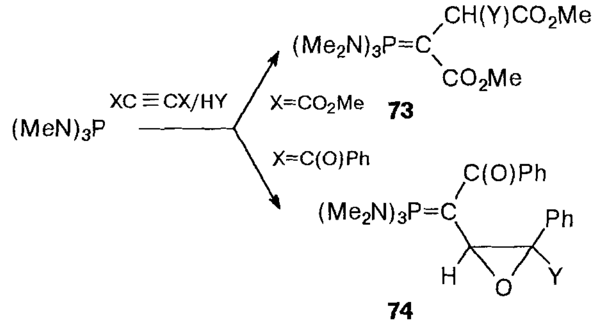
$$(Me_2N)_3P + EtO_2CCH{=}CHCO_2Et \longrightarrow (Me_2N)_3P{=}\underset{\displaystyle CH_2CO_2Et}{\underset{|}{C}}CO_2Et \qquad (5.49)$$



(5.50)

R=H, 4-ClC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$; R^2=Alk$_2$N, R^3=PhNH, Alk$_2$N

In the presence of hydroxylated reagents, the reaction of acetylenedicarboxylate ester with tris(amino)phosphites leads to the formation of ylides. The nucleophilic attack of a P(III) atom on the electron-deficient carbon atom of the activated multiple bond affords a betaine which readily adds alcohol, phenol, or benzoic acid furnishing ylides 73 (Scheme 5.14)[35-37] The reaction of tris(dimethylamino)phosphines with dibenzoylacetylene esters and benzoylacetylenencarboxylic acid in the presence of proton-donating reagents (alcohols, phenols, imides) results in ylides 74, containing an epoxy group, in very high yields. The ylides were isolated as crystalline solids or as liquids distillable in vacuum.[98]



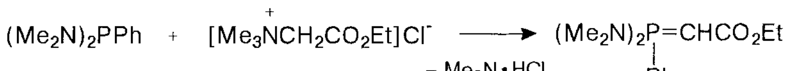
Scheme 5.14

Syntheses of ylide 74 (Scheme 5.14, R = R′ = Ph, HX-phthalimide)

A solution of dibenzoylacetylene (0.01 mol) and phthalimide (0.01 mol) in THF (50 mL) was added dropwise with stirring to a solution of tris(dimethylamino)phosphine (0.01 mol) at −50°C. The solvent was then evaporated under vacuum and dry ether (15 mL) was added to the residue. The yellow precipitate was removed by filtration and dried to give the desired product in quantitative yield, mp 140°C.

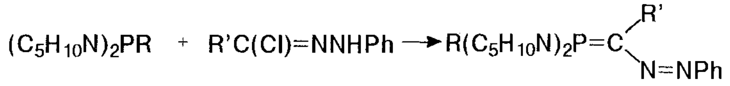
5.2.1.4 Other Synthetic Methods

An interesting example of the synthesis of an ethoxycarbonyl ylide by replacement of trimethylamine in a quaternary ammonium salt with an aminophosphine has been described (Eq.5.51)[99]:



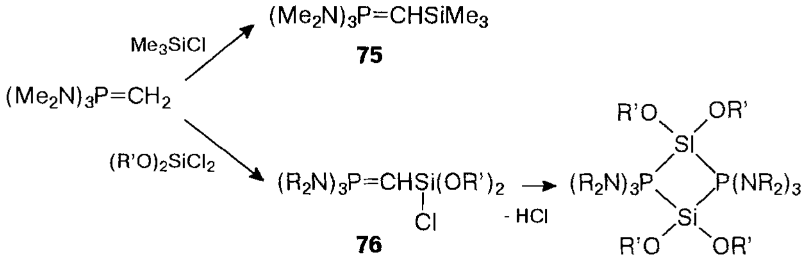
$$(Me_2N)_2PPh + [Me_3\overset{+}{N}CH_2CO_2Et]Cl^- \xrightarrow[-\,Me_3N\cdot HCl]{} (Me_2N)_2\underset{Ph}{\overset{}{P}}=CHCO_2Et \qquad (5.51)$$

The amides of tervalent phosphorus acids react with *C*-ethoxycarbonyl- and *C*-acetyl-*N*-arylnitrileimines with the formation of stable azomethylene-phosphonium ylides (Eq.5.52)[100]:



$$(C_5H_{10}N)_2PR + R'C(Cl)=NNHPh \longrightarrow R(C_5H_{10}N)_2P=C\genfrac{}{}{0pt}{}{R'}{N=NPh} \qquad (5.52)$$

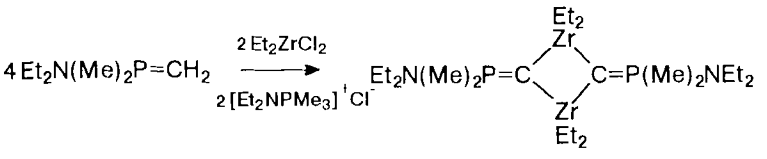
Reaction of tris(dialkylamino)phosphonium methylide with chlorides of the Group IV elements results in transylidation and the formation of C-element-substituted ylides **75**,**76** (Scheme 5.15)[80–82]:



Scheme 5.15

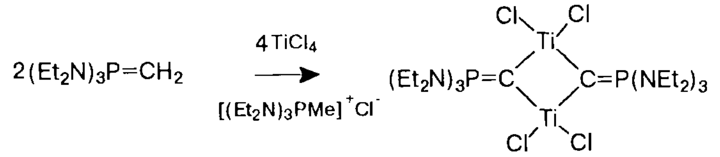
The transylidation of bis(diethylamino) methylphosphonium methylide with diethylzirconium dichloride results in the four-membered cyclic bis-ylide 77 stabilized by two zirconium atoms on the ylide carbon atom; this compound was isolated as yellow monoclinic crystals (Eq.5.53)[101].

Similar ylides **78** bearing titanium at the ylidic carbon atoms have been obtained by reaction of titanium tetrachloride with tris(diethylamino) phosphonium methylide; their structure has been determined by X-ray crystallography. The central fragment of bis-ylide **78**, including the four-membered ring, is almost planar; the sum of the angles in the ring is exactly 360°(Eq.5.54)[102]:



(5.53)

77

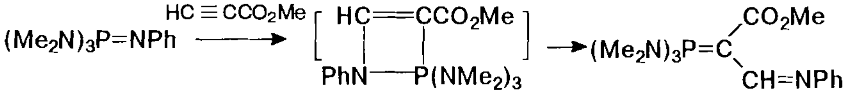


(5.54)

78

Tetrachloro-1,2-bis/tris(diethylamino)phosphonium-2,4-dititano-butan-1,2-diyd **78** (Eq.5. 54)[102]
Titanium tetrachloride (2.30 g, 1.33 mL, 12.1 mmol) in toluene (20 mL) was added at room temperature to a solution of tris(diethylamino)phosphonium methylide (4.76 g, 5 mL, 18.2 mmol) in diethyl ether (30 mL). The reaction solution was then cooled to –78°C and the precipitate of the phosphonium salt (3.8 g, 79mmol) was separated and washed with toluene. The filtrate was evaporated and the residue was recrystallized from toluene. Yield 1 g (69%), mp 180°C.

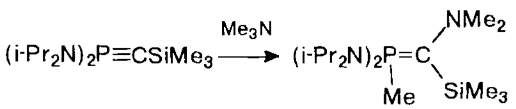
Wolf et al. discovered that tris(dimethylamino)phenyliminophosphorane reacts with acetylenedicarbonic acid esters with the formation of stable ylides **79**. Reaction probably proceeds via the formation of intermediate by [2+2]-addition (Eq.5.55)[103]:



(5.55)

79

Cowley et al. recently reported a very effective synthesis of a P–N ylide by addition of trimethylamine to Bertran's phosphaacetylene (Eq.5.56)[104]:

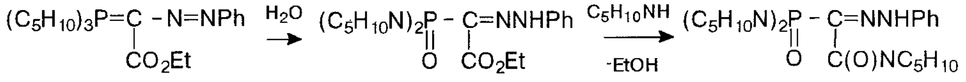


(5.56)

5.2.2 Chemical Properties

5.2.2.1 Reactions with Electrophiles

Ylides with dialkylamino groups on the phosphorus atom are available and are very reactive. The reactivity and stability of dialkylaminophosphonium ylides depend on the substituents on the ylide carbon atom. Dialkylaminophosphonium ylides stabilized by electron-accepting substituents are indeed very stable to hydrolysis. Azomethylenephosphonium ylide **80** hydrolyses only after prolonged heating under reflux in aqueous alcohol (Eq.5.57)[100]:



$$(C_5H_{10})_3P{=}C(CO_2Et){-}N{=}NPh \xrightarrow{H_2O} (C_5H_{10}N)_2P(O){-}C(CO_2Et){=}NNHPh \xrightarrow[-EtOH]{C_5H_{10}NH} (C_5H_{10}N)_2P(O){-}C(C(O)NC_5H_{10}){=}NNHPh$$

80 (5.57)

Ylide **81** does not change even when heated to 140°C for 4 h in 50% KOH. It is, however, active in the Wittig reaction (Eq.5.58)[76]:

$$(Et_2N)_3P{=}CHC(O)NEt_2 \xrightarrow[(Et_2N)_3PO]{4\text{-}O_2NC_6H_4CHO} 4\text{-}O_2NC_6H_4CH{=}CHC(O)NEt_2 \qquad (5.58)$$

81

Non-stabilized and semi-stabilized dialkylaminophosphonium ylides, in contrast, are readily hydrolyzed and are oxidized by atmospheric oxygen (Scheme 5.16)[76]:

$$PhCH{=}CHPh \xleftarrow[-(Et_2N)_3PO]{O_2} (Et_2N)_3P{=}CHPh \xrightarrow{4\text{-}O_2NC_6H_4CHO} 4\text{-}O_2NC_6H_4CH{=}CHPh$$

Scheme 5.16

Ylides with methylene groups react with chloro-containing electrophiles, producing new types of dialkylaminophosphonium ylides **82,83** in high yields. Reaction proceeds with a 2:1 (compound **82**) or 6:1 ratio of reagents (compound **83**), because one or three molecules of ylide are necessary for dehydrochlorination of the intermediate phosphonium salt (Scheme 5.17)[73]:

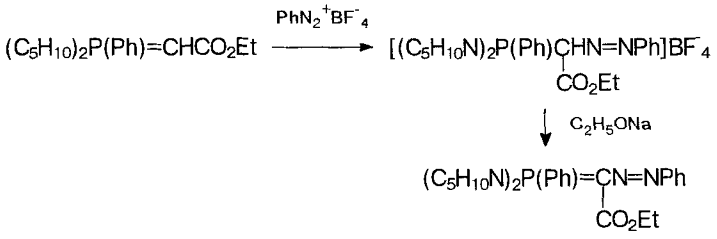
$$(Me_2N)_3P{=}CHPR_2 \xleftarrow{R_2PCl} (Me_2N)_3P{=}CH_2 \xrightarrow{PCl_3} [(Me_2N)_3P{=}CH]_3P$$

82 **83**

R=Me, Et, EtO, Me$_2$N

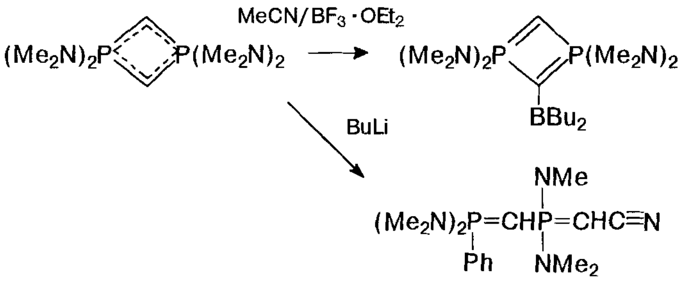
Scheme 5.17

Diazonium salts couple directly with dialkylaminophosphonium ylides. Phenyldiazonium fluoroborate reacts with an ylide to form a phosphonium salt which can be converted into a new ylide by treatment with sodium ethoxide (Scheme 5.18)[76]:



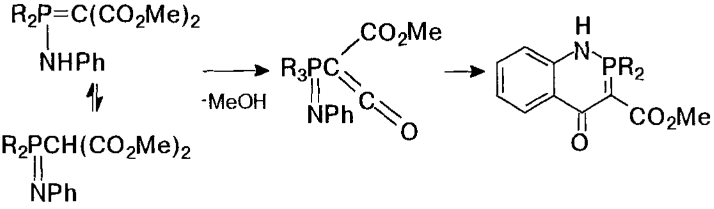
Scheme 5.18

Reaction of tetra(dimethylamino)diphosphetane with acetonitrile in dimethoxyethane at 30°C for 40 min. results in the ylide in modest yield[105]. Tetra(dimethylamino) diphosphetane adds boron trifluoride etherate with the formation of a betaine which on treatment with butyllithium is converted into a C-boron substituted cyclic ylide (Scheme 5.19)[106]. Various reactions of diphosphetane have been described[105–108]. Anilinophosphonium bis(alkoxycarbonyl)methylides, which are stable under normal conditions, evolve alcohol on heating to 150–180°C and are converted into 2-phospha-4-quinolones.



Scheme 5.19

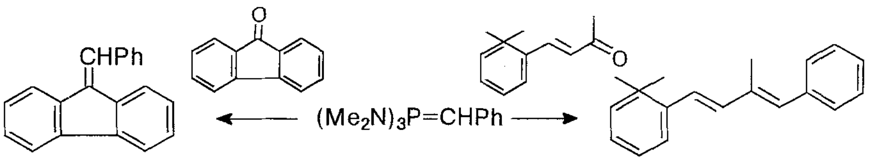
The elimination of the alcohol results in the formation of the ketene, the cyclization of which the *ortho* position of the benzene ring gives rise to 2-phospha-4-quinolone (Eq.5.59)[16]:



(5.59)

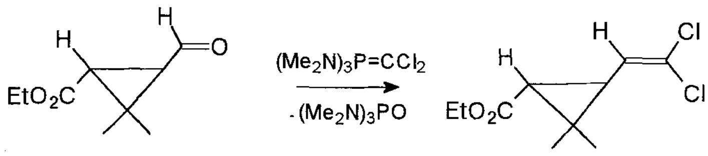
5.2.2.2 P-N Ylides in the Wittig Reaction

Dialkylaminophosphonium ylides are more reactive than triphenylphosphonium ylides in the Wittig reaction. The electron-donating dialkylamino group reduces the electron-accepting properties of the phosphonium group, as a result of which the negative charge on the ylide carbon atom increases. On reaction with the strongly nucleophilic dialkylaminophosphonium ylides, even inactive ketones are converted into olefins and in reactions with reactive carbonyl compounds there is a significant increase in the yields of olefins. The use of dialkylaminophosphonium ylides usually gives satisfactory results when triphenylphosphonium ylides are unsuitable (Scheme 5.20).



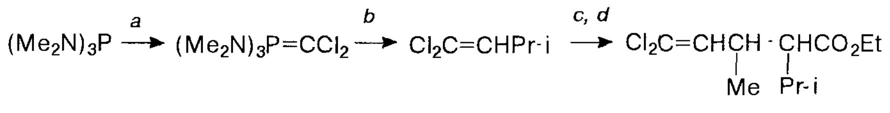
Scheme 5.20

The compounds $(Me_2N)_3P{=}CF_2$ and $(Me_2N)_3P{=}CCl_2$, generated in situ from $(Me_2N)_3P$ and carbon tetrahalides, are good sources of the trifluoromethylene and dichloromethylene groups in reactions with inactive ketones (Scheme 5.20)[99]. $(Me_2N)_3P{=}CCl_2$ generated in situ from $(Me_2N)_3P$ and bromotrichloromethane is highly reactive toward active ketones. Olefination of ethyl-*cis-trans*-caronaldehyde with this ylide affords the derivative of chrysanthemic acid—an analog of the natural insecticide permethrin—in high yield (Eq.5.60)[100]:



(5.60)

Reaction of tris(dimethylamino)phosphonium dichloromethylide with isobutyric aldehyde affords dichlorisopent-1-ene which react with *N*-bromosuccinimide to produce 1,1-dichloroallylbromide. This reacts smoothly with O-silylated ketene acetals with the formation of esters of 5,5-dichloro-2-(1-methylethane)-4-pentinoic acids with the properties of the pyrethroids (Eq.5.61)[95]:

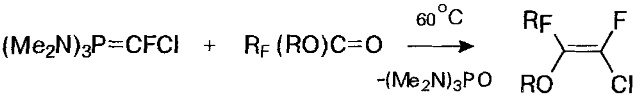


$$(Me_2N)_3P \xrightarrow{a} (Me_2N)_3P{=}CCl_2 \xrightarrow{b} Cl_2C{=}CHPr\text{-}i \xrightarrow{c,\,d} Cl_2C{=}CH\underset{\displaystyle Me}{\underset{|}{C}}H\text{-}\underset{\displaystyle Pr\text{-}i}{\underset{|}{C}}HCO_2Et \qquad (5.61)$$

a=BrCCl3; b=i-PrCHO; c=NBS; d=AlkCH=C(Et)OSiMe3

C-Fluoro-substituted ylides are highly active in the Wittig reaction with non-activated ketones. Reactions of tris(dimethylamino)phosphonium difluoromethylide with diethylketone, acetophenone, cyclohexanone, and propiophenone affords good yields of difluoroolefins (Eq.5.62)[88]. Reaction can be performed in situ or with preliminary preparation of olefination solution[91,92]. Reaction of the tris(dimethylamino) phosphonium fluorochloromethylide with fluoroalkyl-carboxylates proceeds stereoselectively, with the formation preferentially of *Z* isomers of alkylpolyfluoroalkenyl esters (Eq.5.63). Application of $(Me_2N)_3P{=}CFCl$ instead of $Ph_3P{=}CFCl$ considerably increases the yields of perfluoroalkenyl esters in the Wittig reaction.[88]

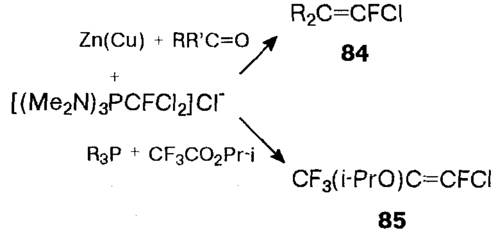
$$(Me_2N)_3P{=}CF_2 + RR'C{=}O \xrightarrow{20^{\circ}\,C} RR'C{=}CF_2 + (Me_2N)_3PO \tag{5.62}$$



(5.63)

$R_F{=}CF_3$, CHF_2, $CFCl_2$, C_2F_5, C_3F_7; R=Me, Et, i-Pr

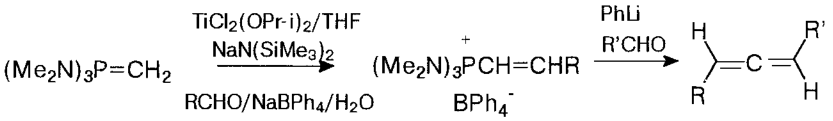
P–N ylides containing halogen atoms on the phosphorus react with aldehydes and with non-symmetrical ketones, to provide *Z* and *E* olefins in approximately equal proportions. Phosphonium salts in the presence of a zinc-copper couple react with carbonyl compounds with the formation of 1-chloro-1-fluoroalkenes **84** (Scheme 5.21). Reaction proceeds in THF or triglyme, in which yields of olefins are higher than in polar aprotic solvents (DMFA or benzonitrile). With aldehydes and activated ketones the yields of olefins are ~100%; with acetophenone ~70%. P–N ylides react with perfluoroalkyl-carbonic acid esters at 60°C to afford olefins **85** in 21–95% yields.[91] The dechlorination of the salt with triphenylphosphine or tris(dimethylamino) phosphine in the presence of isopropyltrifluoroacetone produces predominantly the *Z* isomer of 1-chloro-2-propoxyperfluoropropene (Scheme 5.21):[91,92]



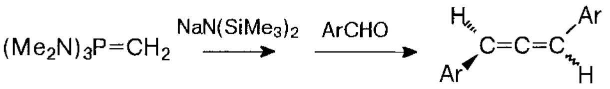
R=Ph, C_6H_{13}, CF_3; R'=H, Ph, CF_3, Me, AlkO

Scheme 5.21

Reynolds and coworkers developed a convenient route to the synthesis of aromatic allenes starting from P–N ylides and carbonyl compounds in the presence of titanium derivatives (Eq. 5.64, 5.65)[89,90]:



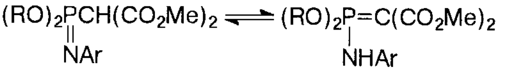
(5.64)



(5.65)

5.2.2.3 Phosphazo–Ylide Tautomerism

Phosphazo compounds containing a mobile hydrogen atom at the α carbon atom exist in tautomeric equilibrium with ylides bearing an amino group on the phosphorus atom (*triad carbon–nitrogen prototropic tautomerism*) (Eq.5.66):

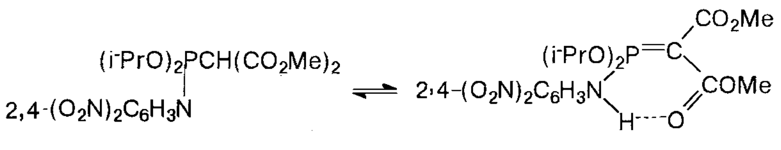


$$(RO)_2\underset{\underset{\text{NAr}}{\|}}{P}CH(CO_2Me)_2 \rightleftharpoons (RO)_2\underset{\underset{\text{NHAr}}{|}}{P}=C(CO_2Me)_2$$

A **B**

(5.66)

The phosphazo–ylide tautomeric equilibrium **A** $\rightleftharpoons$ **B** follows the rules of the acid–base prototropic equilibrium to shift towards the more weakly acidic tautomer[63,109]. The introduction of more electron-accepting substituents to the nitrogen atom of the N–P–C triad increases the content of the phosphazo-form and. conversely, electron-accepting substituents on the carbon atom favor the formation of the ylide form **B**. Depending on the substituents on the nitrogen and carbon atoms, the phosphazo–ylide equilibrium **A** $\rightleftharpoons$ **B** can be displaced towards the preferential formation of one tautomer, or forms **A** and **B** can both be present in a solution (Eq.5.67).



(5.67)

The ratio of the forms **A** and **B** depends on the temperature and the solvent. The migration of the proton between the nitrogen and carbon atoms in the N–P–C triad occurs readily and interconversion of the tautomers **A** $\rightleftharpoons$ **B** takes place comparatively rapidly. Study of the thermodynamics of the phosphazo-ylide tautomerism showed that the tautomeric equilibrium **A** $\rightleftharpoons$ **B** is influenced by two opposed factors. On the one hand, the conversion of the phosphazo form into the ylide form results in an energy gain ($\Delta H = -6 \pm 0.6$ kcal mol^{-1}) but the rigidity of the molecule increases (because the ylide form is fixed by a strong intramolecular hydrogen bond) and the entropy diminishes ($\Delta S = -21 \pm 2$ e.u.). According to the equation $\Delta G = \Delta H - T\Delta S$, the equality of ΔH and $T\Delta S$ determines the equilibrium position. The presence of a strong intramolecular hydrogen bond has been confirmed by infrared and ^{1}H NMR spectroscopy (Eq.5.67).

5.2.2.4 Complexes with Transition Metals

P–N ylides with high nucleophilicity and basicity form stable complexes with transition metal halides. Tris(dimethylamino)phosphonium methylide adds halides of Group IV metals (germanium, tin, lead), and also palladium and platinum halides to form complexes bearing monodentate ylidic ligands on inner orbitals and halogens on outer orbitals (Eq.5.68, Eq.5.69):

$$(Me_2N)_3P{=}CH_2{+}MCl \longrightarrow [(Me_2N)_3PCH_2]^+MCl^- \qquad (5.68)$$

$$(Me_2N)_3P{=}CH_2{+}PtI_4 \longrightarrow [(Me_2N)_3P^+CH_2]_4PtI^-_4 \qquad (5.69)$$

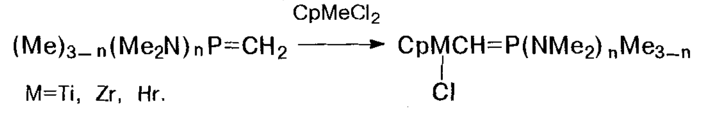
Yamamoto and coworkers synthesized complexes of the tris(dimethylamino) methylide with different metals halides (copper, silver, gold) (Eq.5.70)[110a] and Roesky et al reported complexes with Mo, W, and Nb[110b].

$$m(Me_2N)_3P{=}CH_2 + MCl_n \longrightarrow [(Me_2N)_3\overset{+}{P}CH_2MCH_2\overset{+}{P}(NMe_2)_3]\,2Cl^- \qquad (5.70)$$

$m=2,3$; M= Cu, Ag, Zn, Cd, Hg

Chloride of bis[methyl tris(dimethylamino)phosphonium]gold (Eq.5.70)[110a]
Triphenylphosphinegold chloride (0.36 g, 0.727 mmol) and the ylide (0.39 g, 2.2 mmol) were added to dry benzene (20 mL) under nitrogen and the mixture was stirred for 1 h at room temperature. The white precipitate of the complex was removed by filtration, washed with dry benzene, and dried under vacuum. Yield 0.33 g (77.3%).

The properties of P–N ylide complexes, in particular their spectroscopic characteristics, are similar to those of the corresponding triphenylphosphonium ylide complexes. The P–N ylide complexes differ in their high hydrolytic stability. Especially stable are ylidic complexes of gold which are soluble in water and in organic solvents and stable in air. [110a] Schmidbaur et al. prepared the metallocene ylides of titanium, zirconium, and hafnium **86** by reaction of (dimethyl-amino)methylphosphonium methylide with bis(cyclopentadienyl)metal dichlorides (Eq.5.71)[111]:

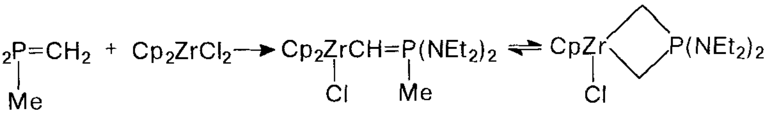


$$(Me)_{3-n}(Me_2N)_nP{=}CH_2 \xrightarrow{CpMeCl_2} Cp\underset{\displaystyle Cl}{\underset{|}{M}}CH{=}P(NMe_2)_nMe_{3-n} \qquad (5.71)$$

M=Ti, Zr, Hr.

86

The zirconium ylide exists in a tautomeric equilibrium with the chelate phosphorus ylide complex, because of prototropic exchange between the methyl group and the ylidic carbon atom. The tautomeric equilibrium **86** $\rightleftharpoons$ **88** depends on the nature of the solvent (Eq.5.72)[102]:



87 **88**

(5.72)

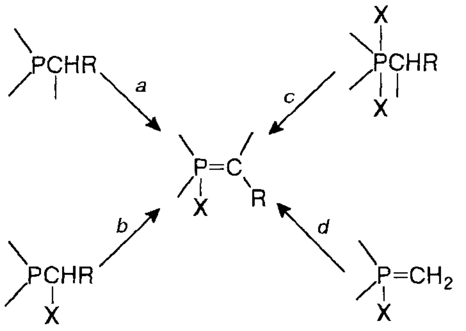
5.3 P-Halogen Ylides

Phosphorus ylides are important reagents widely used in organic synthesis. Among the various types of these compounds synthesized in recent years there is significant interest in P-heterosubstituted phosphorus ylides[1,2,112], particularly ylides containing halogen atoms on phosphorus, or P-Halogenylides as they are usually called. The presence of labile atoms determines the properties of the compounds which are interesting theoretically and preparatively[3-7]. Such important compounds for organic synthesis as phosphorus-containing ketenes, thioketenes, vinylphosphine oxides, and allylphosphine oxides, etc., have been obtained from P-Halogenylides. P-Halogenylides participate in various cycloaddition and heterocyclization reactions and have high phosphorylating capacity. P-Halogenated ylides are also convenient objects for studying important theoretical problems of structure and reactivity of organophosphorus compounds.

5.3.1 Synthesis

Detailed investigations on P-halogenated ylides have enabled the development of convenient methods for their synthesis on the basis of the following conversions.

1. «Oxidative ylidation» of trivalent phosphorus compounds entailing increasing the phosphorus coordination number to four by adding halogen and forming a P=C bond[3]. Such reactions include 1,2-(C→P)-halotropic rearrangements and reactions of tertiary alkylphosphines with carbon tetrahalides to form P-halogenated ylides containing one atom of chlorine or bromine on the phosphorus atom.
2. The formation of a P=C multiple bond in a halophosphorane or halophosphonium salt by an elimination reaction. Various P-chloro and P-fluoro ylides have been synthesized by this means, including some containing several halogen atoms on phosphorus.
3. Reactions of P-halogenated ylides with chlorine-containing electrophiles which proceed with replacement of hydrogen atoms at the α carbon by various groups.



a=CXCl3, X=Br, Cl; *b*= 1,2[P→C]-rearrangement; *c*= i-Pr2NLi; *d*=XCl

Scheme 5.20

The methods listed have enabled P-halogenated ylides of practically any structure to be obtained by simple operations using starting materials available in the laboratory.

5.3.1.1 Rearrangement of α-Haloalkylphosphines into P-Halogenated Ylides

α-Haloalkylphosphines undergo 1,2-(C→P)-halotropic shift to rearrange into P-Halogenylides. The valence of the phosphorus atom is increased as a result of halogen atom migration, a P=C bond is formed and the *α*-haloalkylphosphines **89A** are converted into P-halogenated ylides **89B** (Eq.73)[3,10,113].

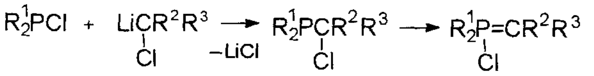
$$R_2P-\underset{\substack{|\\X}}{C}R'_2 \longrightarrow R_2P=\underset{\substack{|\\X}}{C}R'_2 \qquad (5.73)$$

X=Br, Cl

89A **89B**

Halotropy in a P–C diad depends on the substituents R and R′ on the phosphorus and carbon atoms[10]. *α*-Haloalkylphosphines containing electron-accepting substituents on the *α*-carbon atom, stabilizing the ylide function, are readily converted into P-halogenated ylides.

The reaction of diorganochlorophosphines with metallochloromethanes or stabilized by sulfonyl or trimethylsilyl groups proceeds readily (Eq.5.74)[3,10,113,114]. The resulting *α*-chloroalkylphosphines **90** and **91** are very unstable and rearrange into P-chloro ylides at low temperature[114]. For example, *α*-chloroalkylphosphine **90** is stable –110°C in toluene but even at –90°C is converted quantitatively into ylide **91** (Eq.5.74)[114]:



$$R^1_2PCl + Li\underset{\substack{|\\Cl}}{C}R^2R^3 \xrightarrow[-LiCl]{} R^1_2P\underset{\substack{|\\Cl}}{C}R^2R^3 \longrightarrow R^1_2\underset{\substack{|\\Cl}}{P}=CR^2R^3 \qquad (5.74)$$

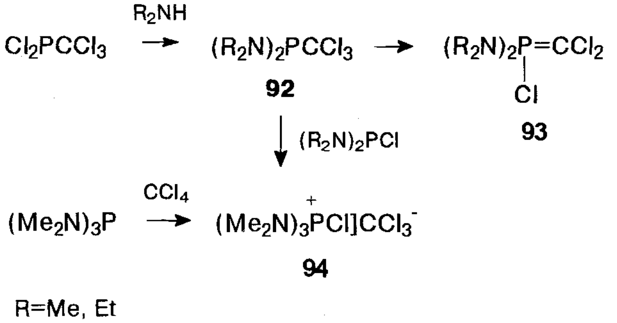
90 **91**

R1=Et, i-Pr, Me2N; R2=SO2CF3, SiMe3, SO2Ph; R3=H, SiMe3, SO2Ph

Di-isopropylchlorophosphonium trifluoromethylsulfonylmethylide **91** (R^1 = *i*-Pr, R^2 = H, $R^3 = SO_2CF_3$, Eq.5.74)[14]
A solution of trifluoromethyl sulfonylchloromethane (0.06 mol) in THF (10 mL) was added dropwise to a solution of diisopropylchlorophosphine (0.05 mol) and triethylamine (0.1–0.15 mol) in THF (10 mL) with cooling and stirring. The reaction mixture was left for 48 h. The triethylamine chlorohydrate was then removed by filtration, the solvent was evaporated, and the residue was distilled. Yield 60%, bp 140°C (0.06 mm Hg), n_D 1.4850.

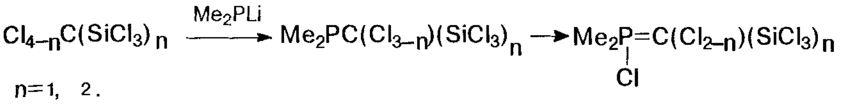
Diethylamino-tert-butyl-chlorophosphonium methylide **91** [R^1 = *t*-Bu(Et_2N), $R^2 = R^3$ = H, Eq.5.74][113]
a) Diethylamine (0.2 mol) in pentane (60 mL) was added dropwise with stirring at –50°C to chloromethyl-*tert*-butyl-chlorophosphine (0.1 mol) in pentane (50 mL),. The temperature was increased to ambient, the precipitate was removed by filtration, and the solvent was evaporated under vacuum. The residue is the spectroscopically pure diethylamino *tert*-butyl(chloromethyl)phosphine **90**, R^1 = *t*-Bu(Et_2N), $R^2 = R^3$ = H]. δ_P 76 ppm.
b) Chloroform (0.05 mol) was added to a solution of diethylamino *tert*-butyl(chloromethyl)phosphine **90** (0.05 mol) in C_6D_6 (20 mL) and the mixture was left for 20–30 min. Ylide **91** was obtained spectroscopically pure ready for chemical reactions.

Compounds of trivalent phosphorus containing a trichloromethyl group are comparatively stable. The bis(dialkylamino)trichloromethylphosphines **92** can be purified by distillation under vacuum and then converted into P-chloro ylides in boiling dichloromethane (Scheme 5.22)[115-117]. The same phosphonites **92** were prepared by reaction of chloro-bis(diethylamino)phosphine with hexamethyltriaminophosphine and carbon tetrachloride. In this instance an ion pair containing the CCl_3^- anion **94** is formed[118]; this can react with chloro-bis(diethylamino)phosphine with the formation of ylide (Scheme 5.22)



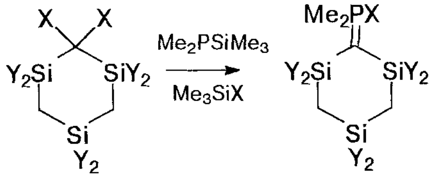
Scheme 5.22

The C-silicon-substituted P-chloro ylides were obtained by reaction of carbosilanes with lithium- or silylphosphines (Eq.5.75, 5.76)[119,120]:



$$\mathrm{Cl_{4-n}C(SiCl_3)_n} \xrightarrow{\mathrm{Me_2PLi}} \mathrm{Me_2PC(Cl_{3-n})(SiCl_3)_n} \longrightarrow \mathrm{Me_2\underset{\displaystyle Cl}{\underset{|}{P}}{=}C(Cl_{2-n})(SiCl_3)_n} \qquad (5.75)$$

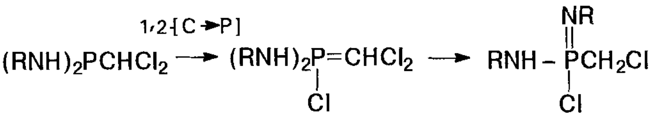
$n=1,\ 2.$



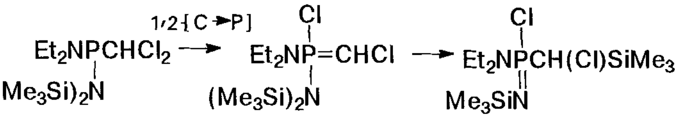
(5.76)

X=Br, Cl; Y=Me, Cl, F

The reaction of C-dihalo-1,3,5-trisilacyclohexanes with silylphosphines under reflux in dimethoxyethane gives P-halogenated ylides (Eq.5.76)[120]. The structures of the P-chloro ylides were proved by X-ray crystallography. Compounds are of planar structure with shortened P=C and Si–C bonds because of delocalization of the negative charge of the ylide carbon atom around the ring[124]. Occasionally, P-chloro ylides, formed by 1,2-(C→P)-chlorotropic rearrangement, undergo prototropic or silylotropic rearrangement to produce iminophosphoranes (Eq.5.77, Eq.5.78)[122–127]:



$$\mathrm{(RNH)_2PCHCl_2} \xrightarrow{1,2\{\mathrm{C}\rightarrow\mathrm{P}\}} \mathrm{(RNH)_2\underset{\displaystyle Cl}{\underset{|}{P}}{=}CHCl_2} \longrightarrow \mathrm{RNH-\overset{\displaystyle NR}{\overset{\|}{\underset{\displaystyle Cl}{\underset{|}{P}}}}CH_2Cl} \qquad (5.77)$$

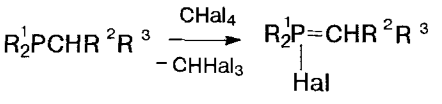


$$\mathrm{Et_2N\underset{\displaystyle Me_3Si)_2N}{\underset{|}{P}}CHCl_2} \xrightarrow{1,2\{\mathrm{C}\rightarrow\mathrm{P}\}} \mathrm{Et_2N\overset{\displaystyle Cl}{\overset{|}{\underset{\displaystyle (Me_3Si)_2N}{\underset{|}{P}}}}{=}CHCl} \longrightarrow \mathrm{Et_2N\overset{\displaystyle Cl}{\overset{|}{\underset{\displaystyle Me_3SiN}{\underset{\|}{P}}}}CH(Cl)SiMe_3} \qquad (5.78)$$

The phosphaethylene was converted into trimethylsilylimidophosphonic chloride in boiling tetrahydrofuran by reaction with excess diethylamine. Seemingly diethylamine adds to the phosphaethylene with the formation of dichloromethylphosphine which rearranges to an unstable P-chloro ylide[125,126].

5.3.1.2 Reactions of Tertiary Alkylphosphines with Positive Halogen Donors

The reaction of tertiary alkylphosphines with compounds bearing positive halogen atoms, for example the carbon tetrahalides, is the best method for the preparation of P-halogenylides[1–8]. The reaction of tervalent phosphorus compounds with carbon tetrahalides was first studied in the last century[128,129], although P-halogenated ylides were not obtained from this reaction for a long time[130–133]. The reaction, which is very sensitive to conditions, proceeded only to the formation of a mixture of compounds that were difficult to identify[133]. Only in 1975–1977 in the laboratory of the author was it established that by observing an appropriate temperature regimen and choice of solvent, tertiary alkylphosphines react with carbon tetrachloride or tetrabromide with the formation of P-halogenated ylides 95 (Eq.5.79)[134,135]:



$$R^1_2PCHR^2R^3 \xrightarrow[-CHHal_3]{CHal_4} R^1_2P(Hal){=}CHR^2R^3$$

95

(5.79)

Table 5.4 P-Halogenylides 95 (Eq.79)

R^3	CR^1R^2	Hal	$CHal_4$	Ref
i-Pr	CH_2	Cl	CCl_4	221
t-Bu	CH_2	Cl	CCl_4	135, 221
t-Bu	CH_2	Br	CBr_4	134, 135
t-Bu	CH_2	Br	$CBrCl_3$	135
t-Bu	$CHAlk(C_1-C_4)$	Cl	CCl_4	135,144
t-Bu	CHPh	Cl	CCl_4	135
t-Bu	CHSMe	Cl	CCl_4	135
t-Bu	CPh_2	Cl	CCl_4	135
t-Bu	$CHSiMe_3$	Cl	CCl_4	135
t-Bu	$CHSiMe_3$	Br	$CBrCl_3$	135
Me	$CHSiMe_3$	Cl	CCl_4	121
Ph	$CHSiMe_3$	Cl	CCl_4	141
Et_2N	CHPh	Cl	CCl_4	159
Et_2N	$CHSiMe_3$	Cl	CCl_4	159, 222
Et_2N	$CHSiMe_3$	Br	$CBrCl_3$	1
Et_2N	$CHSiMe_3$	I	$ClCl_3$	139
Et_2N	CHPr-i	Cl	$ClN(SiMe_3)Bu$-t	113, 201
Et_2N	CPh_2	Cl	CCl_4, $ClNPr$-i_2	201,159
i-Pr_2N	CH_2	Cl	CCl_4	160
i-Pr_2N	CH_2	Br	$CBrCl_3$	202
i-Pr_2N	$C{=}N_2$	Cl	CCl_4	163
i-Pr_2N	CHPh	Cl	CCl_4	160
Et_2N	9-Fluorenylidene	Cl	CCl_4, ,i-Pr_2NCl	201, 180b
Et_2N	9-Fluorenylidene	Br	$CBrCl_3$	180b
Et_2N	9-Fluorenylidene	I	$ClCl_3$	139, 180b
EtO	$CHSiMe_3$	Cl	CCl_4	142
i-PrO	$CHSiMe_3$	Cl	CCl_4	142
i-PrO	$CHCO_2Me$	Br	$CBrCl_3$	143
i-PrO	$C(CO_2Me)_2$	Cl	CCl_4	6
i-PrO	$C(CO_2Me)_2$	Br	CBr_4	6,13
i-Pr	$C(CO_2Me)_2$	Br	$CBrCl_3$	20
Et	$CHSO_2CF_3$	Cl	CCl_4	6,14,137
Ph	$C(SO_2Ph)_2$	Br	CBr_4	6,10

Di-tert-butylchlorophosphonium methylide **95** (R^3 = *t*-Bu, R^1 = R^2 = H, Hal = Cl, Eq.5.79)[135,221]

Di-*tert*-butyl(methyl)phosphine (6.4 g, 0.04 mol) in pentane (30 mL) was placed in a 100-mL, one-necked, round-bottomed flask equipped with pressure-equalizing dropping funnel and magnetic stirrer and tetrachloromethane (6.8 g, 0.04 mol) was added dropwise with stirring at −78°C. In the course of the reaction the solution warms to room temperature. The solvent was evaporated under reduced pressure and the residue consisted of spectroscopically pure chloro(di-*tert*-butyl)phosphonium methylide (Yield ~100%), which can be purified by distillation under vacuum. Yield 5.42 g (70%), bp 55°C (0.08 mm Hg), mp 4°C.

Di-tert-butylchlorophosphonium diphenylmethylide **95** (R^3 = *t*-Bu, R^1 = R^2 = Ph, Hal = Cl, Eq.5.79)[135]

a)*A* solution of diphenylmethane *(13.5 g, 0.08 mol) in THF (75 mL) was placed in a 200-*mL flask and a solution of butyllithium (0.08 mol, ~2 mol L^{-1}) in hexane was added dropwise with stirring at −20°C under argon. The solution was stirred for 2 h at room temperature, cooled to −50°C, and a solution of di-*tert*-butylchlorophosphine (14 g, 0.075 mol) in THF (25 mL) was added dropwise with stirring The reaction mixture was stirred for 1 h at +25°C and 0.5 h at +40–45°C. The reaction mixture was then centrifuged to separate lithium chloride, the solvent was removed under reduced pressure, and the residue was distilled under vacuum or recrystallized from hexane. Yield 80–85%.

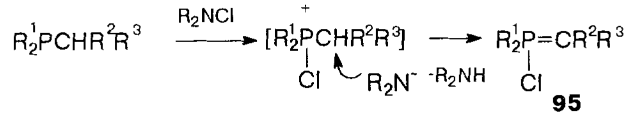
b) A solution of carbon tetrachloride (0.05 mol) in ether (10 mL) was added dropwise at −20°C to a solution of di-*tert*-butyl-diphenylmethylphosphine (9.5 g, 0.03 mol) in ether (50 mL). The solution was then left at room temperature for 0.5 h. The solvent was removed under vacuum and the residue was dissolved in hexane (100 mL) and centrifuged. The solution was concentrated to 75 mL and placed in a freezer. After 2–3 days the crystals formed were removed by filtration. Yield 65%, mp 115°C.

Di-tert-butylchlorophosphonium isobutylide **95** (R^3 = *t*-Bu, R^1 = H, R^2 = *i*-Pr, Hal = Cl) (Eq.5.79)[135]

a) A solution of isobutyllithium (0.5 mol, 1.85 M) in hexane was placed in a dry, 0.5-L, three-necked round-bottomed flask equipped with a mechanical stirrer and a pressure-equalizing dropping funnel. A solution of di-*tert*-butylchlorophosphine (0.45 mol) in hexane (200 mL) was added dropwise at stirring at 0°C under argon. The reaction mixture was stirred for a 0.5 h at room temperature, and was then heated under reflux for 15 min. The precipitate of lithium chloride was removed by filtration and the solvent was evaporated under reduced pressure. The residue was distilled in vacuum to provide the isobutyl-di-*tert*-butylphosphine in 85% yield, bp 85°C (12 mm Hg)

b) A solution of isobutyl-di-*tert*-butylphosphine (0.05 mol) in absolute pentane (50 mL) was placed in a dry 100-mL, round-bottomed flask equipped with a pressure-equalizing dropping funnel and a magnetic stirrer. The flask was cooled to −30°C. and tetrachloromethane (0.055 mol) was added dropwise with stirring. Then the temperature of the reaction mixture rose to room temperature and the reaction mixture was left at room temperature for 0.5 h. The solvent was evaporated and the residue was distilled under reduced pressure. Yield 90%, bp 85°C (0.06 mm Hg).

The reaction of tervalent phosphorus compounds with *N*-chloroamides occurs readily in ether or benzene at room temperature to afford P-chloro ylides in high yields (Eq.5.80)[201]:



$$R^1_2PCHR^2R^3 \xrightarrow{R_2NCl} [R^1_2\underset{Cl}{\overset{+}{P}}CHR^2R^3] \xrightarrow[R_2N^-]{-R_2NH} R^1_2\underset{Cl}{P}=CR^2R^3 \quad \mathbf{95} \qquad (5.80)$$

R_2NCl=i-Pr_2NCl, $(Me_3Si)_2NCl$, t-Bu(Me_3Si)NCl.

Bis(diethylamino)chlorophosphonium diphenylmethylide **95** (R^3 = Et_2N, R^1 = R^2 = Ph, Hal = Cl) (Eq.5.80)[201]

A solution of *N*-chlorodiisopropylamine (2.7 g, 0.02 mol) in diethyl ether (5 mL) was added dropwise with stirring to a solution of bis(diethylamido) diphenylmethylphosphonite (6.84 g, 0.02 mol) in ether (10 mL) at 0°C.The reaction mixture was left to stand for 1 h at ambient temperature, the solvent was evaporated, and the residue was recrystallized from hexane. Yield 90%, mp 98°C.Yellow–orange crystalline solid.

Diethylamino-tert-butyl-chlorophosphonium isobutylide **95** (R_2^1 = *t*-Bu(Et_2N), R^1 = H, R^2 = *i*-Pr, Hal = Cl) (Eq.5.80)[201]

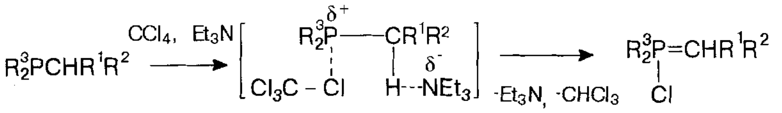
An ether solution of *N*-chloro(*tert*-butyl) trimethylsilylamine (5.37 g, 0.03 mol) was added dropwise with stirring at –70°C to a solution of bis(diethylamino)isobutylphosphine **1** (4.6 g, 0.025 mol) in diethyl ether (15 mL). The temperature was then raised to +20°C and the reaction mixture was left for 30 min. The NMR spectrum (C_6D_6) indicated quantitative yield of ylide **28**, δ_P 94.45 ppm. The solvent was evaporated under reduced pressure to give a colorless liquid, which smoked in air. Yield 95%.

The reaction between the alkylphosphines and *N*-chlorodiisopropylamine resulting in P-Halogenylides evidently proceeds via formation of chlorophosphonium intermediates. Increased of proton mobility on the α carbon atom of alkylphosphines and steric hindrance in the *N*-chloroamides favors the deprotonation of the intermediate by the anion NR_2^-. Thus the activity of *N*-chlororoalkylamides increases in the sequence:

Et_2NCl < *i*-Pr_2NCl < $(Me_3Si)_2NCl$ < *t*-Bu(Me_3Si)NCl

The reaction of tertiary alkylphosphines with carbon tetrahalides (CCl_4[134,135], $CBrCl_3$, CBr_4[135–138], $ClCl_3$[139]) is usually performed in pentane, diethyl ether[134–138], or dichloromethane[141] below 0°C. Reaction with carbon tetrachloride occurs below 0°C, with CBr_4 and $CBrCl_3$ at –70°C. The reaction of tertiary alkylphosphines with *N*-haloamides proceed at room temperature. The yields of P-halogenated ylides are very high. P-Halogenylides can be used without isolation from the reaction mixture for preparative work, which appreciably simplifies handling. In this case it is sufficient to add carbon tetrachloride to the alkylphosphine in ether to obtain a reagent which is very reactive and ready to use[14]. However where necessary P-halogenated ylides may be purified by distillation under vacuum or by crystallization from inert solvents[142–145]. The substituents R^1 and R^2 in the compound can be electron-acceptors, groups increasing the CH-acidity[136,138,141–143], electron-neutral, or electron-donating groups[134,135,138,140]. Compounds of trivalent phosphorus, containing, on the α carbon atom, alkyl groups, hydrogen atoms, or trimethylsilyl or phenyl groups, which stabilize the ylide function, interact most actively with carbon tetrahalides. Yields of ylides obtained in this way are very high[134–136,140]. Strong electron-accepting groups on the α-

carbon atom can reduce the nucleophilicity of the trivalent phosphorus atom because the rate of their interaction with carbon tetrahalides is reduced. For example, the introduction of one, two, or three atoms of chlorine or bromine on the α carbon atom of tertiary alkyl phosphines successively slows reaction with carbon tetrachloride down to a complete stop[159]. Electronegative alkoxycarbonyl or arylsulfonyl groups on the α carbon atom of tertiary alkylphosphines also reduce the rate of interaction of the trivalent phosphorus atom with carbon tetrachloride[136,142]. The reaction rate can, however, in this instance be increased by the addition to the reaction medium of tertiary amines, the catalytic action of which is explained by participation in the formation of an intermediate reaction complex **96** (Eq.5.81)[136,146]:

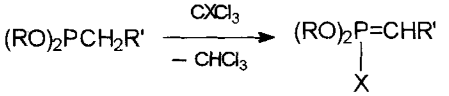


$$R^3_2PCHR^1R^2 \xrightarrow{CCl_4,\ Et_3N} \left[\begin{matrix} \overset{\delta+}{R^3_2P} & \text{—} & CR^1R^2 \\ \vdots & & \mid\ \delta^- \\ Cl_3C-Cl & & H\cdots NEt_3 \end{matrix}\right] \xrightarrow[-Et_3N,\ -CHCl_3]{} R^3_2P(Cl){=}CHR^1R^2 \quad (5.81)$$

96

$CR^1R^2{=}CHSO_2CF_3,\ C(SO_2Ph)_2,\ CHCO_2Me,\ C(CO_2Me)_2;\ R^3{=}Alk,\ Ph,\ AlkO$

Tertiary alkylphosphines containing alkyl, phenyl, or dialkylamino groups on the trivalent phosphorus atom react readily with carbon tetrahalides (Table 5.4)[5,140,141,145,147]. Esters of alkylphosphonous acids react slowly even with excess carbon tetrachloride at 20°C ($R' = SiMe_3$, 14 h) whereas with CBr_4 or $CBrCl_3$ they react in ether at −70°C and give high yields of P-bromoylides (Eq.5.82)[136–138,142,146]:

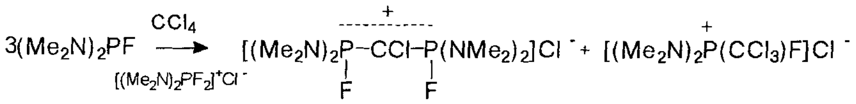


$$(RO)_2PCH_2R' \xrightarrow[-\ CHCl_3]{CXCl_3} (RO)_2P(X){=}CHR' \quad (5.82)$$

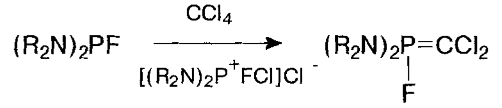
$R{=}Et,\ i{-}Pr;\ R'{=}SiMe_3,\ CO_2Me.$

Diisopropoxychlorophosphonium trimethylsilylmethylide (R= *i*-Pr, R'= $SiMe_3$, Eq.5.82)[142] Carbon tetrachloride (7–8 g) was added dropwise to a solution of diisopropyl trimethylsilylmethylphosphonite (7.2 g, 0.03 mol) in diethyl ether (20 mL) at 0°C. The temperature of reaction mixture was raised to room temperature and the mixture was left for 1 h. Volatile products and solvent were removed under reduced pressure and the residue was distilled under vacuum. Yield 86%, bp 65°C (0.06 mm Hg).

Acid chlorides and bromides of trivalent phosphorus do not react directly with carbon tetrahalides although fluorotetraalkyldiaminophosphines react slowly with carbon tetrachloride at a ratio of 1:3 (R = Me) or 2:1 (R = Et, *n*-Pr) to give P-fluoroylides and phosphonium salts (Eq. 5.83, Eq.5.84)[148,149] The reaction of tertiary alkylphosphines with excess carbon tetrachloride in the presence of chloro-bis(dimethylamino) phosphine leads to the formation of P-chloro ylide phosphonium salts **97** (Eq.5.85)[135]:

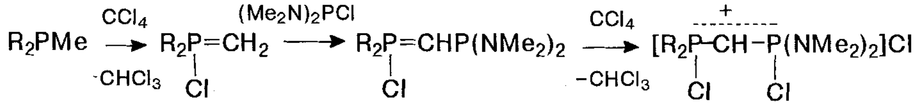


$$3(Me_2N)_2PF \xrightarrow[{[(Me_2N)_2PF_2]^+Cl^-}]{CCl_4} [(Me_2N)_2\underset{F}{P}-CCl-\underset{F}{P}(NMe_2)_2]^+Cl^- + [(Me_2N)_2P(CCl_3)F]^+Cl^- \qquad (5.83)$$



$$(R_2N)_2PF \xrightarrow[{[(R_2N)_2P^+FCl]Cl^-}]{CCl_4} (R_2N)_2\underset{F}{P}=CCl_2 \qquad (5.84)$$

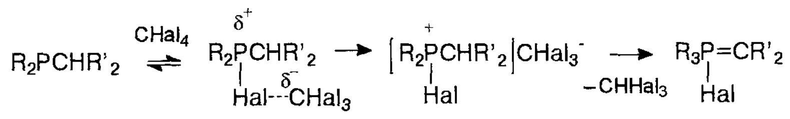
R=Et, i-Pr



$$R_2PMe \xrightarrow[-CHCl_3]{CCl_4} R_2\underset{Cl}{P}=CH_2 \xrightarrow{(Me_2N)_2PCl} R_2\underset{Cl}{P}=CHP(NMe_2)_2 \xrightarrow[-CHCl_3]{CCl_4} [R_2\underset{Cl}{P}-CH-\underset{Cl}{P}(NMe_2)_2]^+Cl^-$$

R=t-Bu, Et$_2$N **97** (5.85)

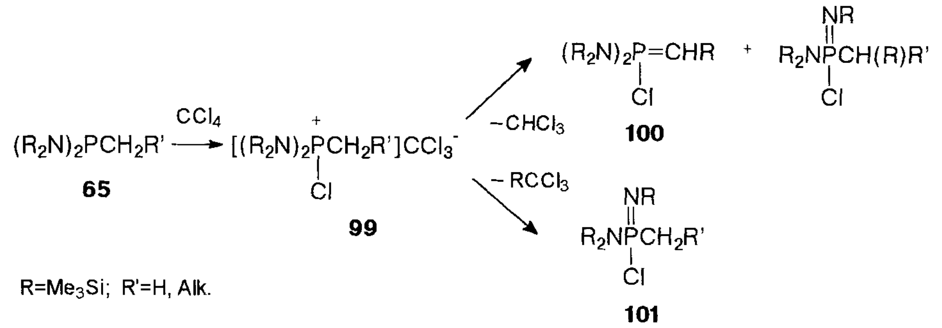
The mechanism of the reaction of tertiary alkylphosphines with CHal$_4$ (Eq.5.86)[12] is evidently of ionic character, as is the reaction of the triphenylphosphine with methane tetrahalogenides[150–153]. The reaction proceeds via the formation of the intermediate complex **98** of tertiary phosphine with CHal$_4$ which is then converted into quasiphosphonium salt **99** containing the trichloromethyl anion. The highly basic CHal$_3^-$ anion deprotonates the α-carbon atom of the phosphonium salt **99**, the CH-acidity of which is fairly high because of the strong positive inductive effect of the phosphonium group, as a result of which haloform is eliminated and a P-halogenated ylide is formed[135,154]. The reaction mechanism was proved by reaction of sterically hindered tri-*tert*-butylphosphine with carbon tetrabromide resulting in a phosphonium salt containing a tribromomethyl anion, which is stable at low temperature (–120°C in pentane) (Eq.5.86):



$$R_2PCHR'_2 \overset{CHal_4}{\rightleftharpoons} R_2\underset{Hal\cdots\overset{\delta^-}{C}Hal_3}{\overset{\delta^+}{P}}CHR'_2 \rightarrow [R_2\underset{Hal}{\overset{+}{P}}CHR'_2]CHal_3^- \xrightarrow[-CHHal_3]{} R_3\underset{Hal}{P}=CR'_2 \qquad (5.86)$$

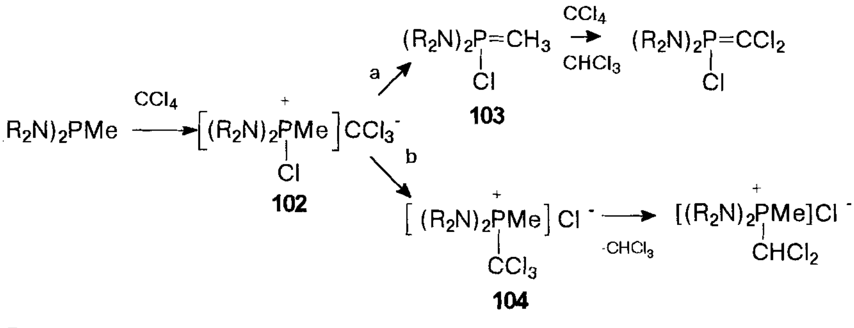
98 **99**

The direction of the reaction of compounds of trivalent phosphorus with carbon tetrahalides and the character of the resulting products depends on the solvent polarity (Scheme 5.23)[155]: Thus, Neilson and coworkers[156] have shown that the reaction of aminoalkylbis (trimethylsilyl)phosphines **65** with carbon tetrachloride in non-polar solvents furnishes P-chloroylides **100**, whereas in dichloromethane the reaction results in imino phosphoranes **101**. The solvent polarity affects on the solvation of the intermediate ion pair **99**, which eliminates chloroform or trimethylsilyltrichloromethane:



Scheme 5.23

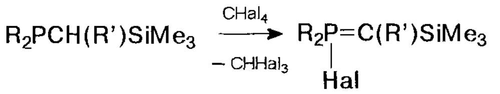
Under some conditions the reaction of trivalent phosphorus compounds with carbon tetrahalides can occur with the formation of trichloromethylphosphonium salts[157–159]. As shown in Scheme 5.24, the reaction of bis(diethylamino)methylphosphine with excess carbon tetrachloride occurs simultaneously in the two directions *a* and *b*, as a result of which a certain quantity of phosphonium salt **104** is formed in addition to ylide[159]. Branched groups on the phosphorus atom hinder attack of $CHal_3^-$ on the intermediate phosphonium cation **102.** Therefore, in contrast with bis(diethylamino) methylphosphine, bis(diisopropylamino)methylphosphine, reacts with carbon tetrachloride to give P-chloro ylide **103** in quantitative yield[160]:



Scheme 5.24

Tertiary alkylphosphines containing bulky *t*-butyl or isopropyl groups are smoothly converted into P-chloro ylides. The groups mentioned not only facilitate ylide formation but also increase their stability[112,134,135].

Tertiary alkylphosphines containing trimethylsilyl groups on the α carbon atom react readily with carbon tetrahalides to give very high yields of ylides **105** (Eq.5.87)[121,135,138–142,147]:

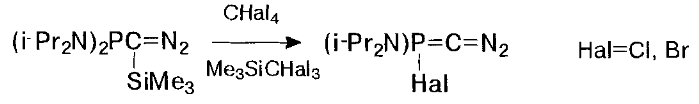


$$\mathrm{R_2PCH(R')SiMe_3} \xrightarrow[-\,\mathrm{CHHal_3}]{\mathrm{CHal_4}} \mathrm{R_2}\underset{\mathrm{Hal}}{\mathrm{P}}\mathrm{=C(R')SiMe_3} \qquad (5.87)$$

105

Hal=Br, Cl; R=Me, i-Pr, t-Bu, Me2N, Et2N, EtO, i-PrO; R'=SiMe3, Ph

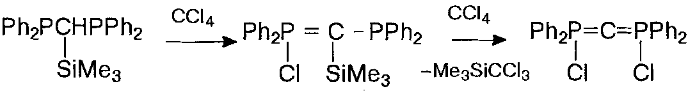
Compound **106** reacts with carbon tetrahalides to produce P-halogenated ylides containing a diazo group on the ylide carbon atom (Eq.5.88)[163,164]. The P-chloro ylides are stable in solution for several days and are very reactive.



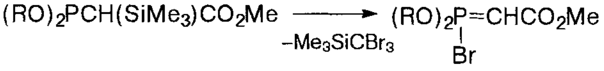
$$\mathrm{(i\text{-}Pr_2N)_2P}\underset{\mathrm{SiMe_3}}{\mathrm{C}}\mathrm{=N_2} \xrightarrow[\mathrm{Me_3SiCHal_3}]{\mathrm{CHal_4}} \mathrm{(i\text{-}Pr_2N)}\underset{\mathrm{Hal}}{\mathrm{P}}\mathrm{=C=N_2} \quad \mathrm{Hal=Cl,\ Br} \qquad (5.88)$$

106

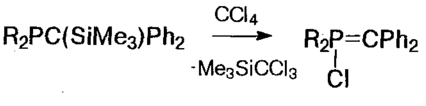
Trivalent phosphorus compounds containing trimethylsilyl groups on the α carbon atom react with carbon tetrahalides with elimination of trihalotrimethylsilylmethane (Eq.5.89–91)[161,162]:



$$\mathrm{Ph_2P}\underset{\mathrm{SiMe_3}}{\mathrm{C}}\mathrm{HPPh_2} \xrightarrow{\mathrm{CCl_4}} \mathrm{Ph_2}\underset{\mathrm{Cl}}{\mathrm{P}} = \underset{\mathrm{SiMe_3}}{\mathrm{C}} - \mathrm{PPh_2} \xrightarrow[-\mathrm{Me_3SiCCl_3}]{\mathrm{CCl_4}} \mathrm{Ph_2}\underset{\mathrm{Cl}}{\mathrm{P}}\mathrm{=C=}\underset{\mathrm{Cl}}{\mathrm{P}}\mathrm{Ph_2} \qquad (5.89)$$



$$\mathrm{(RO)_2PCH(SiMe_3)CO_2Me} \xrightarrow[-\mathrm{Me_3SiCBr_3}]{} \mathrm{(RO)_2}\underset{\mathrm{Br}}{\mathrm{P}}\mathrm{=CHCO_2Me} \qquad (5.90)$$



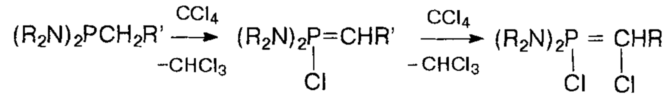
$$\mathrm{R_2PC(SiMe_3)Ph_2} \xrightarrow[-\mathrm{Me_3SiCCl_3}]{\mathrm{CCl_4}} \mathrm{R_2}\underset{\mathrm{Cl}}{\mathrm{P}}\mathrm{=CPh_2} \qquad (5.91)$$

R=Et2N, i-Pr2N, Et, i-Pr

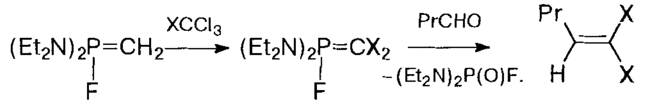
Bis(chlorodiphenylphosphonium)methandiid (Eq.5.89)[162]

A solution of trimethylsilylbis(diphenylphosphino)methane (4.6 g, 10 mmol) in dichloromethane (15 mL) was placed in a 100-mL round-bottomed flask and carbon tetrachloride (4.6 g, 30 mmol) was added dropwise. The color of the reaction mixture turns bright yellow. The reaction mixture was left for 50 min at room temperature and the solvent was evaporated. The residue was mixed with pentane (40 mL) and the solid was removed by filtration and washed with pentane (10 mL). Yield 4.1 g (90%), dec. 150°C.

P-Chloro ylides formed by reaction of trivalent phosphorus compounds with carbon tetrachloride can react with a second molecule of CCl_4 to exchange hydrogen atoms for chlorine atoms on the α carbon atom. Thus reaction of bis(dialkylamino) alkylphosphines with excess carbon tetrachloride gives C-chloro-substituted P-chloro ylides in yields of 70–80% (Eq.5.92)[159,165]. Exchange of hydrogen atoms on the ylide carbon atom for chlorine or bromine occurs on reaction of P-fluoroylides with carbon tetrachloride or tetrabromide in ether at –10 to +20°C (Eq.5.93). C-Halo-substituted ylides have been used in the synthesis of 1,1-dihaloolefins[159].



$$(R_2N)_2PCH_2R' \xrightarrow[-CHCl_3]{CCl_4} (R_2N)_2\underset{\displaystyle Cl}{P}{=}CHR' \xrightarrow[-CHCl_3]{CCl_4} (R_2N)_2\underset{\displaystyle Cl}{P} = \underset{\displaystyle Cl}{C}HR' \qquad (5.92)$$



(5.93)

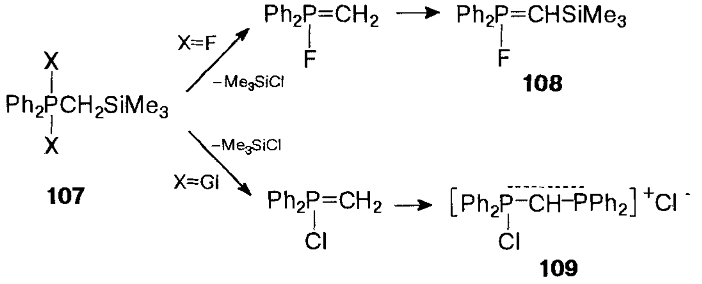
$R_2N=Et_2N$, $C_5H_{10}N$; R=H, Pr, i-Pr, Cl; X= Br, Cl

Bis(diethylamino)chlorophosphonium 1-chloro-2-methylpropylide (Eq.5.92)[159]
Carbon tetrachloride (0.06 mol) was added dropwise to a solution of bis(diethylamido) isobutylphosphonic acid (0.02 mol) in pentane (25 mL) at -20°C. The temperature was increased to 20°C and the reaction mixture was stirred for 15 min. The solvent was then removed under reduced pressure and the residue distilled under vacuum to give a bright yellow, readily hydrolyzed liquid. Yield 70%, bp 105°C (0.01 mm Hg).

The reactivity of P-halogenated ylides with carbon tetrachloride is appreciably reduced by introducing electron-accepting groups on to the ylide carbon atom thus reducing its nucleophilicity[159].

5.3.1.3 Synthesis of P-Halogenated Ylides from Halophosphoranes

A comparatively simple method for the preparation of P-Halogenylides is the elimination of X = Hal, H, or Me_3Si from halophosphoranes or halophosphonium salts [5,146,147]. Difluorotrimethylsilylphosphorane **107**, X = F, eliminates fluorotrimethylsilane at room temperature with the formation of P-fluoroylide, which enters into a transylidation reaction with difluorophosphorane **107** to produce C-silicon-substituted P-fluoroylide **108** (Scheme 5.25)[166].



Scheme 5.25

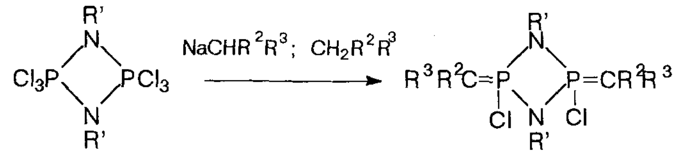
Dichlorophosphorane **107**, X = Cl, on reaction with hexachloroethane is converted into the ylide-phosphonium salt **109**. The different behavior of P-chloro- and P-fluoroylides is seemingly explained by the instability of diphenylchlorophosphonium methylide[167]. The dimerization of this ylide resulting from dehydrochlorination of dichloromethyldiphenylphosphorane with triphenylphosphonium dichloromethylide proceeds in a similar manner (Scheme 5.25)[168].

Polychlorophosphoranes react with bis(arylsulfonyl)methanes in the presence of triethylamine by forming phosphonium salts to give P-chloroylides **110** with one or two chlorine atoms on the phosphorus atom (Eq.5.94)[169,170].

$$\mathrm{Ph_nPCl_{5-n}} \xrightarrow[\mathrm{Et_3N}]{\mathrm{CH_2(SO_2R)_2}} \mathrm{Ph_nP(Cl_{4-n})CH(SO_2R)_2} \xrightarrow[-\mathrm{Et_3N\cdot HCl}]{\mathrm{Et_3N}} \mathrm{Ph_nP(Cl_{3-n})=C(SO_2R)_2} \qquad (5.94)$$

n=1, 2; R=CF_3, C_6H_4X-4, X=H, Me, MeO, Cl **110**

Salman and coworkers reported that reaction of dimers of trichlorophosphazo compounds with sodium acetoacetic ester in boiling benzene proceeds with the formation of P-chloro ylides **111** (Eq 95)[171]:

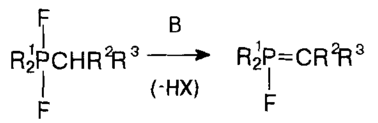


111

(5.95)

R^2=CO_2Et, R^3=COMe (a); R^2=Ph, R^3=Cl (b)

In several instances dihalophosphoranes are not converted into P-halogenated ylides on treatment with organometallic compounds. The main obstacle to the successful preparation of P-halogenated ylides on this manner is the competing substitution of the halogen on the phosphorus by an alkyl group. Nevertheless dehydrohalogenation of difluorophosphoranes with butyllithium or lithium hexamethyldisilazane proceeded quite smoothly and enabled the preparation of P-fluoroylides containing various substituents R^1, R^2, and R^3 on the phosphorus and carbon atoms of the P=C bond. The reaction must be performed in ether at 0°C, because reduction of the temperature to –60 to –80°C severely reduced the yields and purity of the compounds (Eq.5.96, Table 5.5)[166,172]:



$$\mathrm{R^1_2\underset{F}{\overset{F}{P}}CHR^2R^3} \xrightarrow[(-\mathrm{HX})]{\mathrm{B}} \mathrm{R^1_2\underset{F}{P}=CR^2R^3} \qquad (5.96)$$

R^1,R^2=H, Alk, Ar, Cl; R^2=H, Alk, Ar, Cl;
B=BuLi, i-Pr_2NLi, $(Me_3Si)_2NLi$, Et_3N

Bis(diethylamino)fluorophosphonium methylide (R = Et_2N, $R^1 = R^2 = H$) (Eq.5.96, Table 5.5)[219]

A solution of bis(diethylamino)methyl difluorophosphorane (0.05 mol) in pentane (20 mL) was placed under nitrogen in a 100-mL, one-necked, round-bottomed flask equipped with a dropping funnel and a magnetic stirrer and a solution of butyllithium in hexane (27.5 mL, 2.0 M) was added dropwise with stirring at 0–5°C. After warming to room temperature the reaction mixture was left for 1 h. The precipitate of lithium fluoride was then removed by filtration, the solvent was removed under reduced pressure, and the residue was distilled under vacuum. Yield 70%, bp 35°C (0.08 mm Hg).

Bis(diethylamino)fluorophosphonium fluorenylide (Eq.5.96, Table 5.5)[180b]

Method a) Triethylamine (0.1 mol) was added at 0°C to a solution of difluorophosphorane **5** (0.05 mol) in diethyl ether (15 mL) and the mixture was stirred for 30 min. The precipitate was removed by filtration, the filtrate was evaporated, and the residue was recrystallized from hexane–benzene (10:1). Yield 60%, mp 95°C.

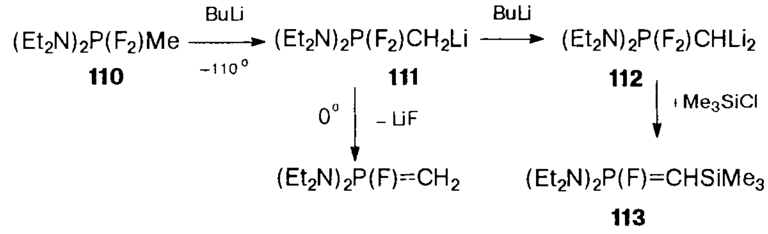
Method b) Zinc fluoride (0.15 mol) was added to a solution of P-chloro ylide **1** (0.005 mol) in benzene (5 mL) and the mixture was stirred for 24 h at room temperature. The reaction mixture was then filtered, evaporated to dryness, and the residue was recrystallized from benzene–hexane (1:10). Yield 45%, mp 95°C.

Reaction of the difluorophosphorane **110** with butyllithium gives the C-lithium substituted difluorophosphorane **111** which eliminates lithium fluoride at –20 to 0°C but is stable at lower temperatures.

Table 5.5 P-Fluoroylides (Eq.96)

R^1	R^2	R^3	Yield (%)	b.p.°C/mmHg	Ref
Me_2N	H	H	48.5	42/10	173
Et_2N	H	H	70	35/0.08	4a,172
Et_2N	Ph	H	76.3	97-115/ 0.008	173
Me_2N	$SiMe_3$	H	48.5	78/10	173
Et_2N	$SiMe_3$	H	85	70/0.06	4a,166
Me_2N	CO_2Me	H	58.2	47-50/0.001	173
t-Bu	H	H	80	65/12	172
t-Bu	Pr	H	65	65/0.08	172
t-Bu	Ph	H	70	100/0.08	4a
t-Bu	Me	Et	65	45-48/10	180c
Et_2N	Me	H	60	35/0,08	172
Et_2N	Me	Me	80	70/0.08	166
Et_2N	Pr-i	H	60	60/0,08	172
Et_2N	Cl	Cl	70	40/0.05	180d
Et_2N	Me	Cl	70	80/0.06	165
Et_2N	$CR^2R^3{=}CAr_2$		60	mp 95	180b
Et_2N	Br	Br	90	-	165
t-Bu,EtO	Pr-i	H	60	75/10	180e
t-Bu,BuO	Pr-i	H	70	102/15	180e
t-Bu,PhO	Pr-i	H	70	86/0.06	180e

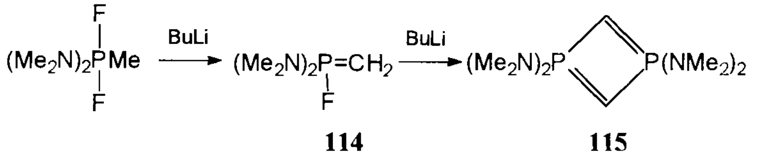
At −60°C and below, compound **111** is readily metallated by reaction with a second molecule of butyllithium with the formation of the dilithio-substituted difluorophosphorane **112** (Scheme 5.26). The reaction of difluorophosphorane **110** with two equivalents of chlorotrimethylsilane led to the formation of the C-silylated P-fluoroylide **113** in high yield[166].



Scheme 5.26

Bis(diethylamino)fluorophosphonium trimethylsilylmethylide **113** (Scheme 5.26)[166]
A solution of bis(diethylamino)methyldifluorophosphorane (0.05 mol) in tetrahydrofuran (50 mL) was placed in a 100 mL one-necked, round-bottomed flask, cooled to −100°C and a solution of butyllithium in hexane (0.2 N, 0.12 mol) was added dropwise at stirring. The reaction mixture was left at −100 to −80°C for 2 h and chlorotrimethylsilane (0.125 mol) was added. The temperature was gradually increased to +20°C. The precipitate of lithium fluoride was separated, the solvent was evaporated, and the residue was distilled in vacuum to give a colorless mobile liquid. Yield 85%, bp 70°C (0.06 mm Hg).

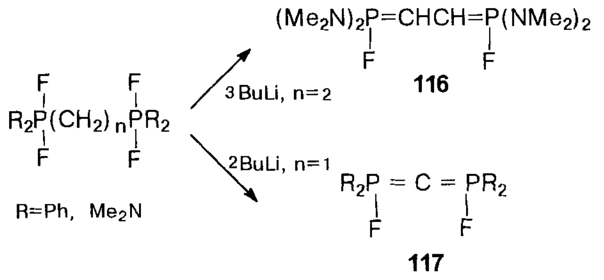
Butyllithium reacts with bis(dimethylamino)methyldifluorophosphorane in a 1:1 ratio in pentane at −80°C to afford the P-fluoroylide **114**[173,174] whereas reaction of the difluorophosphorane with two equivalents of butyllithium in pentane at −95°C results in the formation of the diphosphacyclobutadiene **115** (Eq.5.97)[84,85]. X-ray crystallography revealed the planar structure of the four membered ring of the molecule with completely equal P–C bonds[174,175,178].



(5.97)

Diphosphacyclobutadiene **115** is a reactive compound and readily participates in various cycloaddition reactions[105-108].

The reaction of bis(difluorophosphoranyl)ethane with butyllithium furnishes the bis-ylide **116** in good yield (Scheme 5.27)[176]. The carbodiphosphoranes **117** were obtained by reaction of bis(difluorophosphoranyl)methane with butyllithium. The structure of the carbodiphosphorane **117** was shown by X-ray crystallography (Scheme 5.27)[177,178].



Scheme 5.27

Dehydrofluorination of dialkyltrifluorophosphoranes or dialkylamino-alkyltrifluorophosphoranes with butyllithium or lithium amide leads to the formation of ylides bearing two fluorine atom on the phosphorus atom. (Eq.5.98, Table 5.6)[179,180]: P,P-Difluoroylides are stable distillable under vacuum, colorless liquids. They are very easily hydrolyzed by atmospheric moisture, but can be stored below 0°C when carefully protected from exposure to air

$$R^1P(F_3)CHR^2R^3 \xrightarrow[-R_2NH,-LiCl]{R_2NLi} R^1P(F_2){=}CR^2R^3 \tag{5.98}$$

R^1=s-Bu, t-Bu, Et2N; $CR^2R^3=CH_2$, CHPr, CHPr-i, C(Me)Et;
$R_2NLi = (i\text{-}Pr_2N)_2NLi$, $(Me_3Si)_2NLi$

Table 5.6. P, P-Difluoroylides (Eq.98)

R^1	R^2	R^3	δ_P,ppm	$^1J_{PF}$, Hz	Ref
Et2N	H	H	66.13	1025	180
Et2N	Pr	H	59.40	1045	180
Et2N	Pr	Me	53.13	1054	180
t-Bu	Pr	Me	97.22	1058	180
t-Bu	i-Pr	H	89.80	1050	179
t-Bu	Me	Et	89	1050	180
s-Bu	Me	Et	79.5	1040	179
Et2N	Cl	Cl	52.0	1070	180d

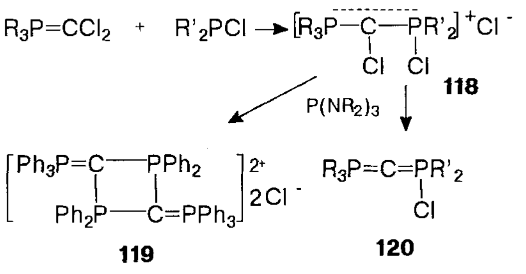
Diethylaminodifluorophosphonium butylide (Eq.5.98, Table 5.6)[180a]

A solution of (diethylamino)butyltrifluorophosphorane (0.02 mol) in THF (10 mL) was placed in a 100-mL one-necked, round-bottomed flask and a solution of lithium diisopropylamide (0.022 mol) in THF (10 mL) was added dropwise with stirring at −20°C. The temperature of reaction mixture was increased to +20°C and the precipitate of lithium chloride was removed by filtration. The solvent was evaporated and the residue was distilled under vacuum. Yield 80%, bp 60°C (12 mm Hg).

Diethylaminodifluorophosphonium dichloromethylide (Eq.5.98, Table 5.6)[180d]

A solution of butyllithium (0.02 mol, 2.3 N) in hexane was added dropwise at −100°C with stirring to a solution of diethylaminotrifluorotrichlormethylphosphorane **11** (0.007 mol) in diethyl ether (20 mL). The mixture was stirred at -30°C for 30 min, then the temperature was increased to +20°C. The mixture was filtered, the solvent was evaporated under vacuum, and the residue was distilled. Yield 70%, bp 40–42°C (0.05 mm Hg).

Appel and coworkers reported that dechlorination of salt **118** with tris (dimethylamino)phosphine in toluene at –78°C gives chloropentaphenylcarbodiphosphorane **119**[181,182] whereas in dichloromethane at room temperature the dimer of product **120** is formed (Scheme 5.28, Table 5.7.)[183,184].

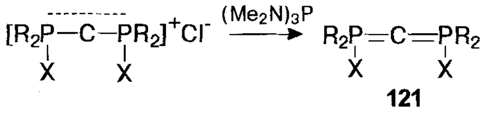


Scheme 5.28

Table 5.7. Carbodiphosphoranes **120** (Scheme 5.28)

R	R'	Yield, (%)	mp,°C	δ_P	Ref
Ph	NMe_2	66	114	31.6;-45.3, $^1J_{PP}$ 94.3	183
Ph	NEt_2	72	123	26.18;-7.70, $^1J_{PP}$ 99.0	183
Me_2N	NMe_2	87	oil	39.52;11.33, $^1J_{PP}$ 153,7	183
Ph	Ph	60	99	2.5;8.7, $^1J_{PP}$ 41.5	181

Symmetrical P-halogen-substituted carbodiphosphoranes **121** were obtained by dechlorination of the halophosphonium salts with tris(dimethylamino) phosphine[185–187]. Carbodiphosphoranes **121** were purified by distillation under vacuum (Eq.5.99, Table 5.8).

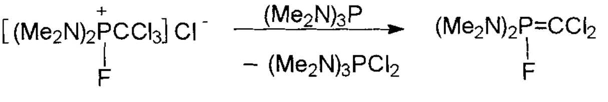


$$[R_2\underset{X}{P}{-}C{-}\underset{X}{P}R_2]^+Cl^- \xrightarrow{(Me_2N)_3P} R_2\underset{X}{P}{=}C{=}\underset{X}{P}R_2 \qquad (5.99)$$

121

R=Me2N, X=F; R=Me2N, Et2N, Pr2N, Ph, X=Cl.

The dehalogenation of trichloromethylphosphonium salts with tris(dimethylamino) phosphine proceeds readily, giving P-halogenated ylides containing a dichloromethylene group in good yield (Eq.5.100)[149]:



$$[(Me_2N)_2\underset{F}{\overset{+}{P}}CCl_3]\,Cl^- \xrightarrow[-\,(Me_2N)_3PCl_2]{(Me_2N)_3P} (Me_2N)_2\underset{F}{P}{=}CCl_2$$

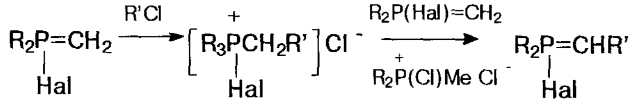
(5.100)

Table 5.8. Dihalogencarbodiphosphoranes **121** (Eq.5.99)

R	X	Yield, (%)	bp°C/p mmHg	δ_P (ppm)	Ref
Me_2N	Cl	60	115-116/0.03	40.68	185
Et_2N	Cl	90	140-142/0.01	31.19	185
Pr_2N	Cl	66	164-165/0.01	31.94	185
Me_2N	F	80	71-73/0.03	41.73, $^1J_{PF}$ 966	185
Ph	F	80	mp 90-93	43.2, $^1J_{PF}$ 1000	177

5.3.1.4 Other Methods for the Synthesis of P-Haloylides

Hydrogen atoms and trimethylsilyl groups on the α carbon atom of P-halogenated ylides can be replaced by reaction with different electrophiles. The reaction of P-chloro- and P-fluoroylides with chlorotrimethylsilane, and chlorides of carboxylic, carbonic, and phosphoric acids proceeds readily to give new P-halogenated ylides[3,112]. Yields of P-halogenated ylides containing trimethylsilyl, acyl, alkoxycarbonyl, or phosphino groups on the α-carbon atom are approximately 50–85% (Eq.5.101)[135,173,188,227-].



$$\underset{Hal}{R_2P}{=}CH_2 \xrightarrow{R'Cl} \left[R_3\underset{Hal}{\overset{+}{P}}CH_2R'\right]Cl^- \xrightarrow[-\,R_2\overset{+}{P}(Cl)Me\,Cl^-]{+\,R_2P(Hal){=}CH_2} \underset{Hal}{R_2P}{=}CHR'$$

(5.101)

Hal=Cl, Br, F; R'=Me_3Si, R'P, R'C(O), AlkOCO

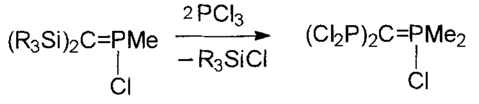
*Diethylamino-tert-*butyl*-chlorophosphoniumtrimethylsilylmethylide* (Eq.5.101)[135]

A solution of chlorotrimethylsilane (0.01 mol) in ether (10 mL) was added to a solution of diethylamino-*tert*-butylchlorophosphonium methylide (0.02 mol) in ether (20 mL) at –30 to –40°C. After warming to room temperature the reaction mixture was left for 30 min. The layer of viscous liquid (chlorophosphonium chloride) was separated and the solvent was evaporated. The residue was distilled under vacuum. Yield 70%, bp 85°C (0.08 mm Hg).

*Di-tert-*butyl*-chlorophosphonium trifluoroacetylmethylide* (Eq.5.101)[227]

A solution of di-*tert*-butyl-chlorophosphonium methylide (0.02 mol) in THF (25 mL) was placed in a 50 mL, one-necked round-bottomed flask and trifluoroacyl chloride (0.01 mol) was added dropwise at –60°C. Then the temperature was raised to room temperature and the reaction mixture was left for 15–20 min. The precipitate of the phosphonium salt was removed by filtration, the solvent was evaporated, and the ylide was extracted from the residue with warm ether. The product was recrystallized, initially from cooled diethyl ether then from pentane. Yield 60%, mp 83–85°C. Colorless solid (needles) hydrolyzed by atmospheric moisture.

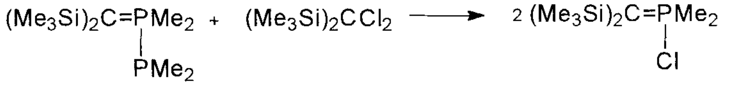
The reaction of C-silylated ylides with phosphorus trichloride in benzene at room temperature furnishes, in good yield, ylides containing two dichlorophosphine groups on the phosphorus atom (Eq.5.102)[189]:



$$\underset{\displaystyle \mathrm{Cl}}{(R_3Si)_2C{=}PMe} \xrightarrow[-\,R_3SiCl]{2\,PCl_3} \underset{\displaystyle \mathrm{Cl}}{(Cl_2P)_2C{=}PMe_2} \tag{5.102}$$

$R_3Si{=}Cl_3Si$, $Cl_2Si(CH_2SiCl_2)_2C$, $Me_2Si(CH_2SiMe_3)_2C$.

A ylide containing a P–P bond was converted in good yield into the P-chloro ylide by reaction with dichlorobis(trimethylsilyl)methane (Eq.5.103)[120]:

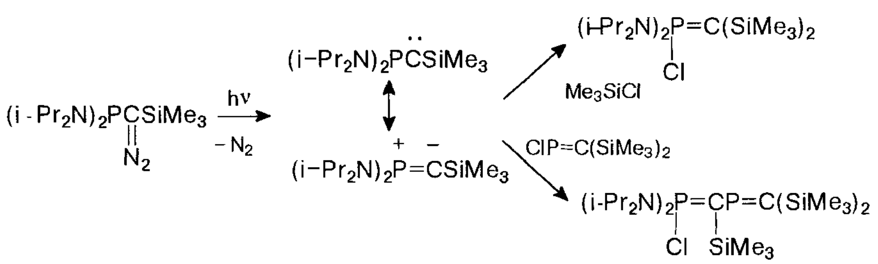


$$\underset{\displaystyle \mathrm{PMe_2}}{(Me_3Si)_2C{=}PMe_2} + (Me_3Si)_2CCl_2 \longrightarrow 2\,\underset{\displaystyle \mathrm{Cl}}{(Me_3Si)_2C{=}PMe_2} \tag{5.103}$$

Ylides with OH groups on the phosphorus, which are prototropic isomers of bis-(arylsulfonyl)methylphosphine oxides, form P-chloro ylides on boiling with phosphorus pentachloride in benzene[170].

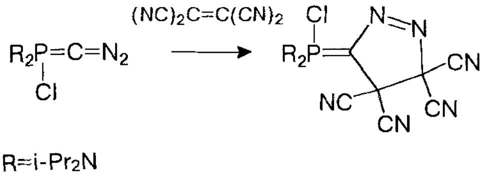
Photolysis, and flash-vacuum pyrolysis, of phosphinodiazomethane afford a stable phosphinocarbene, with some 'phospha-acetylene' character, which was purified by distillation in vacuo[190]. The phosphinocarbene has some of the structure of phosphorus vinyl ylide and therefore readily undergoes addition and cycloaddition reactions, including the formation of phosphorus ylides (Scheme 5.29)

The photolysis of phosphinodiazomethane in benzene solution at room temperature in the presence of an excess chlorotrimethylsilane gives the P-chloro ylide in almost quantitative yield[190–193]. In the presence of chlorophosphaalkene the reaction results in a P-chloro ylide with a dicoordinate phosphorus atom on the α carbon (Scheme 5.29)[194].



Scheme 5.29

The phosphacumulene ylide reacts with tetracyanoethylene forming P-chloro ylides in quantitative yield. These are products of [2+2]-cycloaddition at the diazo group (Scheme 5.30).[15,163]



Scheme 5.30

Bickelhaupt et al. have synthesized a P-iodo ylide by 1,1-addition of methyl iodide to the dicoordinated phosphorus atom. of 1-mesityl-2,2-diphenylphosphaethylene[195].

5.3.2 Physical and Spectral Properties

P-Halogenylides are crystalline substances or liquids. The majority of P-halogenated ylides are colorless and only some of them are colored. For example, fluorenylides are intensely red and diphenylmethylides are an orange color[135].

The stability of P-Halogenylides depends on the nature of the halogen atom: F > Cl > Br >> I. The most stable are P-fluoroylides. They can be stored in an inert atmosphere and are distillable under vacuum without decomposition. The less stable P-chloro ylides can often be distilled under vacuum and are stable when stored in an inert atmosphere at 0°C. The least stable P-bromoylides can be successfully isolated and purified only when they have electron-accepting groups on the α carbon atom. The P-iodo ylides are stable only when they have electron-accepting groups on the α carbon atom[195]. The stability of P-halogenated ylides is increased by increasing the electron-accepting properties of substituents on the α carbon atom, by reducing the negative charge centered on this atom, and by introducing bulky substituents (e.g. *t*-butyl, isopropyl, diisopropylamino groups, etc.) on the phosphorus and carbon atoms, creating steric hindrance. Such substituents screen the P=C bond and hinder nucleophilic attack of the ylide carbon atom at the positively charged phosphorus atom.

The structure of P-halogenated ylides has been investigated in detail by various spectroscopic methods including IR, UV, ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR, and by X-ray crystallography[23,120,174,177,184].

The ^{31}P chemical shifts for P-halogenated ylides are very close to the δ_P values of the corresponding phosphonium salts and depend on the substituents on the phosphorus (to a large degree) and carbon (to a lesser degree), i.e. δ_P 50–70 (R = Alk$_2$N), 40–60 (R = Me), 90–100 (R = *i*-Pr), 95–110 (R = *t*-Bu), 55 (R = Ph), 60 p.p.m. (R = AlkO). (Table 5.9). The signals from phosphorus nuclei of P-halogenated ylides are doublets, $^{1}J_{PF}$ 1000–1100 Hz.

The ^{13}C chemical shifts of the P=C carbon atom are in the region of δ_c 20–80 p.p.m. and are doublets with large values of the $^{1}J_{CP}$ constant of 150–200 Hz, which is in agreement with the carbanion character of the ylide carbon atom.

X-Ray crystallographic analysis shows the effective delocalization of the negative charge on the ylide carbon atom of P-halogenoylides by substituents connected to this atom. The ylide part of the molecules studied has a planar structure[177].

Table 5.9. ^{31}P-NMR Data of P-Chloroylides $R^1_2P(Cl)=CR^3R^4$

R^1_2P	R^3R^4	δ_P, ppm	Ref	R^1_2P	R^3R^4	δ_P, ppm	Ref
i-Pr$_2$P	CH$_2$	95.0	221	Ph$_2$P	CHSiMe$_3$	57.30	141
t-Bu$_2$P	CH$_2$	116.7	135,221	(Me$_2$N)$_2$P	CHPh	62.0	145
t-Bu(Me$_2$N)P	CH$_2$	94.0	221	(Et$_2$N)$_2$P	CHBu-t	63.91	113
t-Bu(Et$_2$N)P	CH$_2$	94.0	221	(Et$_2$N)$_2$P	CHPr-i	62	113
t-Bu(Bu$_2$N)P	CH$_2$	96.0	230	(Et$_2$N)$_2$P	CHPh	62.20	145
(i-Pr$_2$N)$_2$P	CH$_2$	61.00	160	(Et$_2$N)$_2$P	CHSiMe$_3$	71.80	222
t-Bu$_2$P	CHMe	104.0	221	(i-Pr$_2$N)$_2$P	CH$_2$	56.00	113
t-Bu$_2$P	CHEt	101.0	221	(i-Pr$_2$N)$_2$P	CHPr-i	50.50	113
t-Bu$_2$P	CHPr-i	101.5	135	(i-Pr$_2$N)$_2$P	CHBu-t	63	113
t-Bu$_2$P	CHPh	91.0	221	(i-Pr$_2$N)$_2$P	CHSiMe$_3$	61	113
t-Bu$_2$P	CHSiMe$_3$	114.3	221	(i-Pr$_2$N)$_2$P	CHCl	64.0	113
t-Bu$_2$P	CHSMe	109.5	221	(EtO)$_2$P	CHSiMe$_3$	59.0	142
i-Pr$_2$P	CHPh	74.8	145	(EtO)$_2$P	CHCO$_2$Me	59.0	6
(i-Pr$_2$N)$_2$P	C=N$_2$	31	163	(i-PrO)$_2$P	CHSiMe$_3$	59.0	142
Ph(Me)P	C(SiMe$_3$)$_2$	53	147	t-Bu$_2$	CPh$_2$	89	221

5.3.3 Chemical Properties

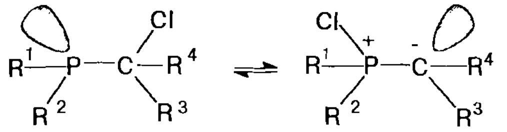
The chemical properties of P-halogenated ylides are very unusual because of the presence in the molecule of a highly polar P=C bond and a labile halogen atom. Characteristic reactions of P-halogenated ylides occur with carbonyl compounds, proceeding with retention of the phosphorus-carbon bond, chlorotropic rearrangements in the P–C diad, conversions with reduction in the phosphorus coordination number, and several other properties not encountered with triphenylphosphonium ylides.

5.3.3.1 Conversions of P-Halogenated Ylides Proceeding with Reduction in the Phosphorus Coordination Number

A significant negative charge is located on the α carbon atom of P-halogenated ylides. Because this weakens the P-Hal bond, transition of a tetracoordinated into a tricoordinated phosphorus atom, which is extremely rare in organophosphorus chemistry, becomes possible.

a) Halotropy in the P-C diad

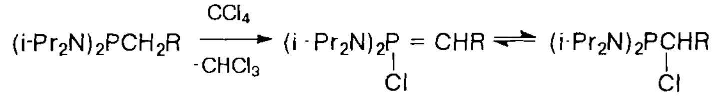
Halogen atoms on the P-C diad are capable of migrating between the phosphorus and carbon atoms as a result of which the interconversion of P-halogenated ylides and α-haloalkylphosphines may be effected. Various examples of 1,2-(P→C)- and 1,2-(C→P)-interconversions of P-chloro ylides and α-chloroalkylphosphines have been described[196–206]. This interconversion **a** $\rightleftharpoons$ **b** is accompanied by the migration of chlorine and the free electron pair between the phosphorus and carbon atoms and by a change in the coordination numbers of these atoms (Eq.5.104).



a b

(5.104)

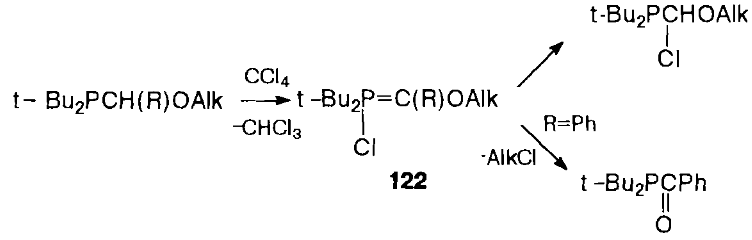
Sterically hindered bis(diisopropylamino)phosphines react with carbon tetrachloride at temperatures below 0°C, being converted quantitatively into P-chloro ylides which, depending on the substituents R, can exist as ylides, can rearrange into α-chloroalkylphoshines, or can give a mixture of ylide and phosphine chlorotropic tautomers (Eq.5.105)[112,197]:



$$(i\text{-}Pr_2N)_2PCH_2R \xrightarrow[-CHCl_3]{CCl_4} (i\text{-}Pr_2N)_2\underset{\displaystyle Cl}{P}=CHR \rightleftharpoons (i\text{-}Pr_2N)_2P\underset{\displaystyle Cl}{C}HR \qquad (5.105)$$

R= H, n-Pr, i-Pr, t-Bu, Ph, SiMe3, Cl

P-Chloro ylides **122** containing an alkoxy group on the α carbon atom rearrange to α-chloroalkylphosphines, by 1,2(P→C)-migration of chlorine, or are converted into acylphosphines with loss of alkyl chloride (Scheme 5.31).



Scheme 5.31

Bis(diisopropylamino)methylphosphines react with excess CCl_4 or $CBrCl_4$ in ether at 0°C to give P-halogenated ylides which readily rearrange into dihalomethylphosphines (Eq.5.106)[159,196]:

$$(R_2N)_2Me \xrightarrow{CXCl_3} (R_2N)_2P(X){=}CH_2 \xrightarrow{CXCl_3} (R_2N)_2P(X){=}CHX \longrightarrow (R_2N)_2PCHX_2 \qquad (5.106)$$

X=Br, Cl; R= i-Pr

Chlorotropic migration depends on substituents on the carbon atom of the P–C diad electron-acceptor substituents shift the chlorotropic equilibrium toward the P-chloro ylide and electron-donating substituents shift the equilibrium toward the chloroalkylphosphonites (Table 5.10)[198,200].

Table 5.10. Effect of substituents at the phosphorus and carbon atoms on the diad phosphorus-carbon chlorotropic rearrangements **a** $\rightleftharpoons$ b.[113]

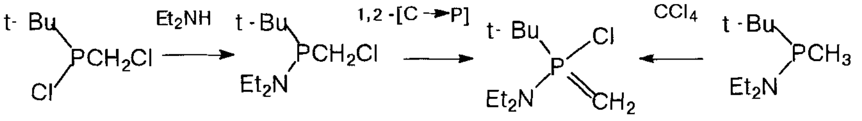
R^1	R^2	R^3	R^4	δ_P (**a**),ppm	δ_P (**b**),ppm	ratio **a** : **b**
Et_2N	Et_2N	Pr-i	H	62	87.8	4:1
Et_2N	Et_2N	Bu-t	H	63.91	85	4:1
Et_2N	Et_2N	Pr-i	Cl	58.50	-	100:0
Et_2N	Et_2N	Bu-t	Cl	52.03	-	100:0
i-Pr_2N	i-Pr_2N	H	H	61	46	0:100
i-Pr_2N	i-Pr_2N	Pr	H	-	53.6	0:100
i-Pr_2N	i-Pr_2N	Pr-i	H	-	50.45	0:100
i-Pr_2N	i-Pr_2N	Bu-t	H	63	52.03	0:100
i-Pr_2N	i-Pr_2N	Ph	H	54.08	-	100:0
i-Pr_2N	i-Pr_2N	$SiMe_3$	H	61	-	100:0
i-Pr_2N	i-Pr_2N	H	Cl	64	46	1:12
Et_2N	t-Bu	Pr-i	H	94.45	-	100:0
Et_2N	t-Bu	H	H	107	76	95:5

*) ratio of chlorotropic isomers in an equlibrium state

Bis(diisopropylamido)dichlorophosphonate (Eq.5.106)

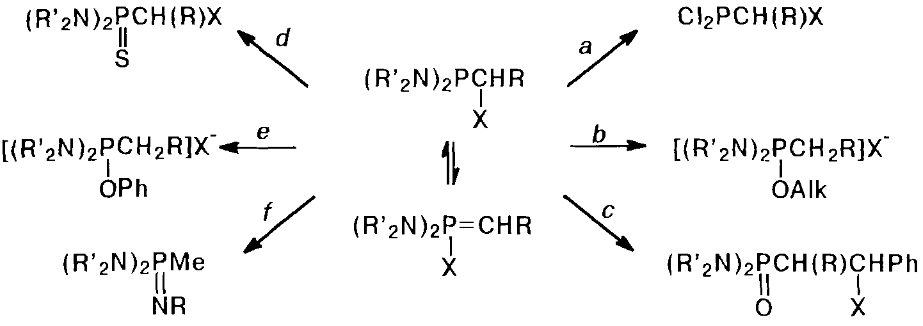
A solution of bis(diisopropylamido)methylphosphonate (0.033 mol) in diethyl ether (30 mL) was cooled to –70°C and carbon tetrachloride (0.15 mol) was added dropwise. After warming to room temperature the reaction mixture was left for 30 min. The solvent was then removed under vacuum and the residue was then dissolved in pentane (60 mL) and filtered. The mother solution was concentrated to 30 mL, cooled to –60°C and left for several hours. A crystalline product was separated. After recrystallization from hexane the desired product was obtained in 70% yield, mp 98.5–99.5°C.

1,2-[(C→P]-Chlorotropic rearrangement of α-chloroalkylphosphines into P-chloro ylides was studied with diethylamino(*tert*-butyl)chloromethylphosphine as an example (Eq.5.107):



(5.107)

The chemical properties of α-chloroalkylphosphines correspond to the existence of a reversible phosphorus–carbon diad chlorotropy (a) $\rightleftharpoons$ (b)[160,198]. As is shown in Scheme 5.32, the α-haloalkylphosphines, compounds of trivalent phosphorus, add sulfur to form α-haloalkylthiophosphonic acid derivatives and are cleaved by hydrogen chloride to afford phosphonic acid. chlorides[160]. Like P-halogenylides, the α-haloalkylphosphines add alcohols and phenols with the formation of R-oxyphosphonium salts, they react with primary alkylamines and aniline to furnish imidophosphonic acid derivatives, and react with carbonyl compounds to give 2-chloroalkylphosphonic acid derivatives[160,198,200].



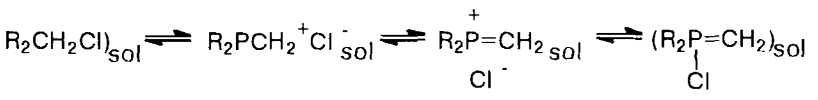
a=HCl, b=AlkOH, c=PhCHO, d=S_8, e=PhOH, f=R'NH_2

Scheme 5.32

Kinetic measurements of 1,2(P→C) and reverse 1,2(C→P) chlorotropic rearrangements showed that these reactions follow a first-order rate equation and depends strongly on solvent polarity. The rate constant for the rearrangement increased in proportion to the increase in ionizing power of the solvent, the influence of the solvent decreasing in the sequence:

$CH_3CN > Cl_2CHCHCl_2 > CHCl_3 > CH_2Cl_2 > C_6H_6 > C_6H_{14}$.

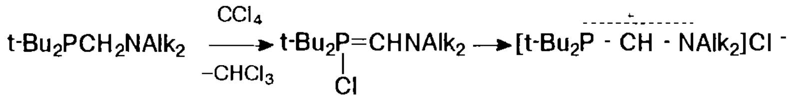
The kinetic characteristics and energetic parameters enable the conclusion that 1,2(P→C)- and 1,2(C→P)-chlorotropic rearrangements proceed in accordance with a monomolecular mechanism, probably via the formation of phosphinium cation **A** as a result of ionization of the P–Cl bond in a P-chloro ylide, or the C–Cl bond in an α-chloroalkylphosphine, solvated by polar solvents (Eq.5.108)[113,160]:



$$R_2CH_2Cl)_{sol} \rightleftharpoons R_2PCH_2{}^{+}Cl^{-}_{sol} \rightleftharpoons \underset{Cl^{-}}{R_2\overset{+}{P}=CH_2}{}_{sol} \rightleftharpoons (R_2\underset{Cl}{P}=CH_2)_{sol} \qquad (5.108)$$

b) Conversion into compounds of tricoordinate pentavalent phosphorus and two-coordinate phosphorus

P-chloro ylides containing a dialkylamino group on the α carbon atom are ionized with cleavage of the P–Cl bond (Eq.5.109). However in this case, as a result of more effective delocalization of the positive charge in the P–C–N triad, stable phosphonium cations **122** are formed and were isolated as crystalline compounds[208].

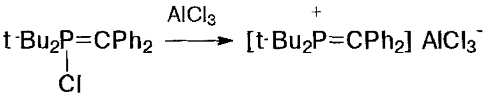


$$t\text{-}Bu_2PCH_2NAlk_2 \xrightarrow[-CHCl_3]{CCl_4} t\text{-}Bu_2\underset{Cl}{P}=CHNAlk_2 \longrightarrow [\overset{+}{\overline{t\text{-}Bu_2P - CH - NAlk_2}}]Cl^{-} \qquad (5.109)$$

122

Compounds **123** are very soluble in polar solvents but dissolve with difficulty in nonpolar solvents. They readily exchange chloride anion for perchlorate anion on reaction with sodium perchlorate in aqueous solution[197]. The structure of phosphonium cations **123** was confirmed by NMR spectroscopy and by X-ray crystallography[206]. The synthesis of other phosphonium cations has been reported. Thus the treatment of an ethereal solution of phosphacarbene with trimethylsilyl triflate resulted in a salt-like product which was isolated as a yellow crystalline substance (Eq.5.110)[57]. The structure of the phosphinium cation was confirmed by NMR and X-ray crystallography. Grutzmacher reported that phosphinium cations can be generated by cleavage of the P–Cl bond in P-chloro ylides with aluminum chloride (Eq.5.111)[209-213]:

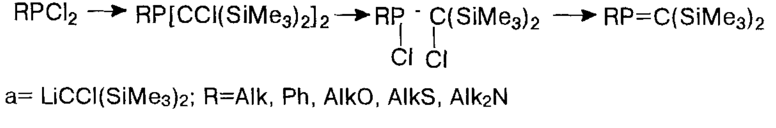
$$(i\text{-}Pr_2N)_2\overset{+}{P}=\overset{-}{C}SiMe_3 \xrightarrow{CF_2SO_2OSiMe_3} [(i\text{-}Pr_2N)_2\overset{+}{P}=C(SiMe_3)_2]CF_3SO_3^- . \qquad (5.110)$$



$$t\text{-}Bu_2\underset{\displaystyle Cl}{\underset{|}{P}}=CPh_2 \xrightarrow{AlCl_3} [t\text{-}Bu_2P=CPh_2]^+ AlCl_3^- \qquad (5.111)$$

1,1-Di-tert-butyl-2,2-diphenylmethylenephosphonium tetrachloroaluminate (Eq.5.111)[212]
Powdered pure freshly sublimed aluminum chloride (0.068 g, 0.05 mol) was mixed with dichloromethane (15 mL) and the suspension was cooled to –75°C and stirred at this temperature for 15 min. A solution of di-*tert*-butylchlorophosphonium diphenylmethylide (2.5 g, 0.045 mol) was added and the mixture was stirred for 15 min at –75°C. Excess aluminum chloride was removed by filtration at –30°C and the solvent was evaporated under vacuum at –30°C to provide the desired product as a solid. Yield approximately 90%. Recrystallization from hexane gave the crystalline product, mp 108–109°C (yellow needles).

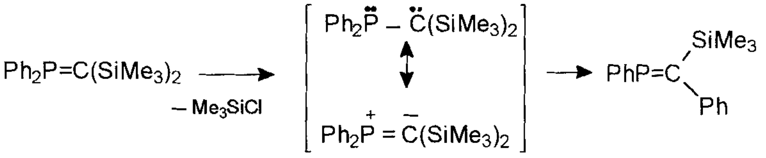
Appel[215,216] obtained organolithium bis(methylene)phosphoranes by dehalogenation of P-chloro ylides with an organolithium compound. (Eq.5.112):



$$RPCl_2 \xrightarrow{a} RP[CCl(SiMe_3)_2]_2 \longrightarrow R\underset{\displaystyle Cl}{\underset{|}{\overset{\displaystyle C(SiMe_3)_2}{\overset{\|}{P}}}}-\underset{\displaystyle Cl}{\underset{|}{C}}(SiMe_3)_2 \xrightarrow{a} RP=C(SiMe_3)_2 \qquad (5.112)$$

a= LiCCl(SiMe3)2; R=Alk, Ph, AlkO, AlkS, Alk2N

Thermolysis of a P-chloro ylide bearing two trimethylsilyl groups at the α carbon is accompanied by migration of a phenyl group to the α carbon atom (a type of Curtius rearrangement) to give rise to the phosphaalkene(Eq.5.113)[217]:



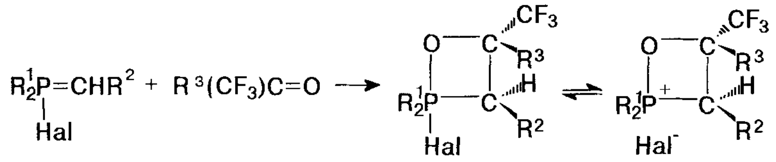
$$Ph_2P=C(SiMe_3)_2 \xrightarrow[-\,Me_3SiCl]{} \left[\begin{array}{c} Ph_2\ddot{P}-\ddot{C}(SiMe_3)_2 \\ \updownarrow \\ Ph_2\overset{+}{P}=\overset{-}{C}(SiMe_3)_2 \end{array}\right] \longrightarrow PhP=C\begin{array}{l} \diagup SiMe_3 \\ \diagdown Ph \end{array} \qquad (5.113)$$

5.3.3.2 Reactions of P-Halogenated Ylides with Carbonyl Compounds

The reactions of P-halogenated ylides with carbonyl compounds are highly unique. P-Halogenylides react with carbonyl compounds 'anomalously' without fission of the phosphorus–carbon bond, which results in phosphorus-containing alkenes. In addition P-Halogenylides form comparatively stable products by [2+2]-cycloaddition of the C=O group to the P=C bond.

a) [2+ 2] Cycloaddition Reactions

P-Chloro- and P-bromoylides react with ketones containing a trifluoromethyl group with the formation of stable [2+2]-cycloaddition products, 2-chloro- or 2-bromo-1,2λ^5-oxaphosphetenes; these were isolated in yields close to quantitative as crystalline substances or as liquids distillable in vacuum (Scheme 5.33)[144,217–219]:



X= Br, Cl; **123C** **123D**

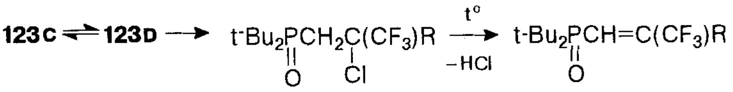
R^1= i-Pr, t-Bu, Et_2N; R^2= H, Me, Ph, R= Ph, C_6H_4OMe-4, C_6H_4F-4

Scheme 5.33

2-Chloro-2,2-di-tert-butyl-4-phenyl-4-trifluoromethyl-1,2-oxaphosphetane (Scheme 5.33) [219]
Phenyltrifluoromethylketone (0.02 mol) was added to a solution of di-*tert*-butylchlorophosphoniummethylide (0.02 mol) in ether (15 mL) at –10 to –5°C. After warming to room temperature the reaction mixture was stirred for 10–15 min The solvent was then removed under vacuum and residue was recrystallized from hexane. Yield 80%, mp 82–84°C (colorless prisms).

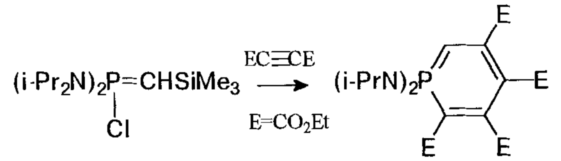
The [2+2]-cycloaddition of P-halogenated ylides to ketones proceeds stereoselectively and leads predominantly to the formation of one of the possible diastereomers of 2-halooxaphosphetanes—the diastereoisomer ratio is within the limits 95:5 to 90:10 [218,219].

2-Halo-1,2λ^5-oxaphosphetanes dissociate in solution at the P–halogen bond with the formation of cyclic phosphonium salts, as a result of which an equilibrium is established between the forms with five- and four-coordinate phosphorus atoms. Dissociation of 2-halooxaphosphetanes is enhanced by reducing the electron-accepting properties of substituents R^3 and also by increasing the solvent polarity[219]. The most stable are 2-halooxaphosphetanes containing strong electron-accepting groups at C(4); these withdraw electron density from the oxygen atom as a result of which the three-center apical bond O–P–Hal is strengthened. For example, 2-chlorooxaphosphetanes containing two CF_3 groups on the α carbon atom, are converted into vinylphosphonates with elimination of hydrogen chloride only at a temperature of 160–190°C[144,219]. The 2-chlorooxaphosphatane (R^1 = t-Bu, R^2 = H, R^3 = p-MeOC$_6$H$_4$) is transformed quantitatively into the 2-chloroalkylphosphine oxide at room temperature On heating chloroalkylphosphine oxide readily eliminates hydrogen chloride to result in the *E* olefin in high yield (Eq.5.114)[144]:

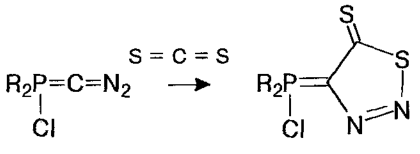


$$\mathbf{123c} \rightleftharpoons \mathbf{123d} \longrightarrow \text{t-Bu}_2\underset{\underset{O}{\|}}{P}CH_2\underset{\underset{Cl}{|}}{C}(CF_3)R \xrightarrow[-HCl]{t^\circ} \text{t-Bu}_2\underset{\underset{O}{\|}}{P}CH{=}C(CF_3)R \qquad (5.114)$$

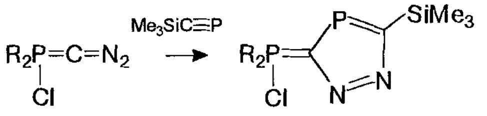
2-Bromooxaphosphetanes are less stable than 2-chlorooxaphosphetanes and are converted into vinylphosphine oxides at room temperature[219,220]. Phosphacumulene ylides react with carbon disulfide forming P-chloro ylides in quantitative yield. These are products of [2+2]-cycloaddition at the diazo group (Eq.5.115–5.117)[15,163,220]:



(5.115)



(5.116)

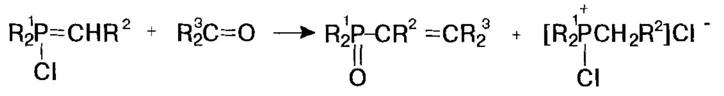


R=i-Pr2N

(5.117)

b) Synthesis of Phosphorus-Containing Alkenes

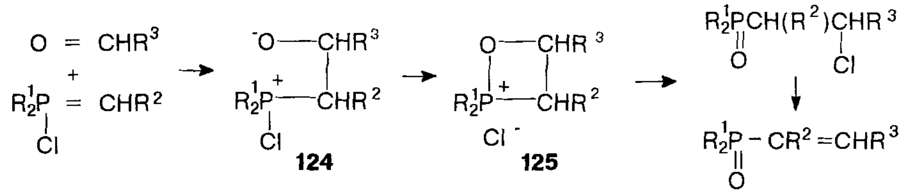
P-Chloro ylides are more reactive than triphenylphosphonium ylides. Unstabilized P-chloro ylides (R^2 = H, Alk) react readily with alkyl- and arylaldehydes below 0°C with the formation of various types of phosphorus-containing alkene[8]. The reaction of P-chloro ylides with aldehydes or ketones proceeds with a 2:1 ratio of the starting compounds to result in phosphorylated olefins (Eq.5.118)[112,144]:



$$R^1_2\underset{\underset{Cl}{|}}{P}{=}CHR^2 + R^3_2C{=}O \longrightarrow R^1_2\underset{\underset{O}{\|}}{P}{-}CR^2{=}CR^3_2 + [R^1_2\overset{+}{\underset{\underset{Cl}{|}}{P}}CH_2R^2]Cl^- \qquad (5.118)$$

R^1=Alk, Alk$_2$N; R^2=H, Me, Ph; R^3_2= Ph$_2$C, Ar(CF$_3$)C.

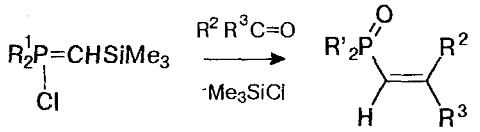
It was established by low-temperature ^{31}P NMR spectroscopy that P-chloro ylides add aldehydes with the formation of betaines **124**, which are then converted into 2-chlorooxaphosphetanes **125**. Compound **125** is strongly dissociated at the P–Cl bond and exists predominantly as a cyclic phosphonium salt. They are stable in solution at –60°C, but when the temperature is increased rearrange into 2-cloroalkylphosphine oxides. The compounds are dehydrochlorinated by excess of the initial P-chloro ylide with the formation of vinylphosphine oxides (Scheme 5.34). Often the reaction of P-chloro ylides with aldehydes occurs with the formation of 2-chloroalkylphosphine oxides which are stable at room temperature and can purified by crystallization from non-polar solvents. On heating they lose hydrogen chloride and are converted in high yield into *E*-vinylphosphine oxides (Scheme 5.34)[221]:



R^1=Alk, Alk$_2$N; R^2=H, Alk, Ph; R^3=Alk

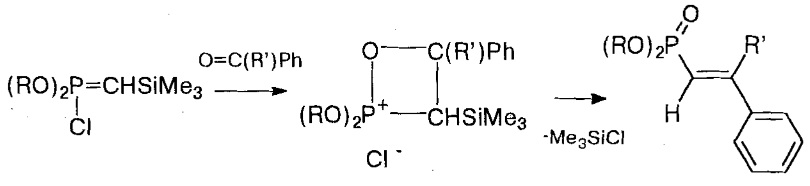
Scheme 5.34

C-Silicon-containing P-chloro ylides react with aldehydes and ketones with elimination of chlorotrimethylsilane. The reaction proceeds with a 1:1 ratio of the initial reactants to give vinylphosphine oxides in high yield (Eq.5.119)[222]: A number of aldehydes, dialdehydes, and ketones have been olefinated with P-chloro ylides. In all cases olefins of *E* configuration were obtained with very good stereoselectivity [112,142,222]:



(5.119)

R^1=Alk, Alk$_2$N; R^2=H, CF_3; R^3=Alk, Ar, CH=CHPh



(5.120)

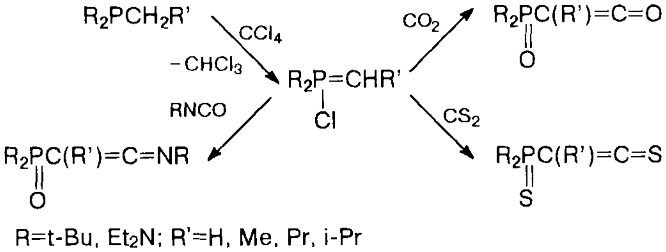
R=Et, i-Pr; R'=H, CF_3o

Bis(diethylamido)sterylphosphonate (Eq.5.119)[222]

Bis(diethylamino)chlorphosphonium trimethylsilylmethylide (0.01 mol) was mixed with benzaldehyde (0.011 mol) and the reaction mixture was left for 14 h at room temperature.

Excess benzaldehyde was removed under a vacuum of 0.05 mm Hg at 100°C and the residue was recrystallized from hexane. Yield 80%, mp 103.5°C.

There is significant preparative interest in the reaction of P-chloro ylides with carbon dioxide, carbon disulfide, and isocyanates leading to the formation of phosphorus-containing ketenes, thioketenes, and ketenimines[134,144]. The reaction of P-chloro ylides with CO_2, CS_2, and RNCO proceeds with an initial ratio of starting materials of 2:1 and leads to the formation of phosphorus-containing heterocumulenes and chlorophosphonium chlorides. Phosphorus-containing heterocumulenes are conveniently obtained preparatively by a 'one-pot' method without isolating P-chloro ylides by sequentially treating tertiary alkylphosphines with CCl_4 initially and then with CO_2, CS_2, or RNCO (Scheme 5.35)[134,140,144,223]:



Scheme 5.35

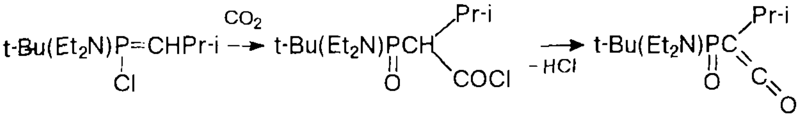
Di-tert-butylphosphinoyl(methyl)ketene (Scheme 5.35)[134]

Di-*tert*-butyl(ethyl)phosphine (17.4 g, 0.1 mol) was dissolved in 50 mL of hexane in a 100-mL one-necked, round-bottomed flask equipped with a magnetic stirrer and a dropping funnel.. Tetrachloromethane (18.73 g, 0.125 mol) was added dropwise with stirring to the mixture at –60°C. The mixture was slowly warmed to room temperature and then again cooled to –60°C and carbon dioxide–ether solution (~0.2 mol CO_2) was added to the reaction mixture. After stirring of the reaction mixture at –60°C for 30 min, it was left to warm to room temperature. The resulting di-*tert*-butylchloro(ethyl)phosphorane was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was distilled under vacuum to furnish the ketene. Yield 7.57 g (70%), bp 98°C (0.06 mm Hg).

Di-tert-butylthiophosphenylpropylthioketene (Scheme 5.35)[144]

Di-*tert*-butyl(isobutyl)phosphine (10.17 g, 0.05 mol) was dissolved in pentane (50 mL) and carbon tetrachloride (8.24 g, 0.055 mol) was added dropwise with stirring at –30°C. After raising the temperature to 0 to 10°C, carbon disulfide (1.9 g 0.025 mol) was added under the same conditions and the mixture was stirred for another 30 min at room temperature. The resulting di-*tert*-butyl(isopropyl)dichlorophosphorane was removed by filtration and the pentane was evaporated. The residue was distilled under vacuum to furnish the desired product. Yield 5.53 g (80%), bp 115°C (0.08 mm Hg).

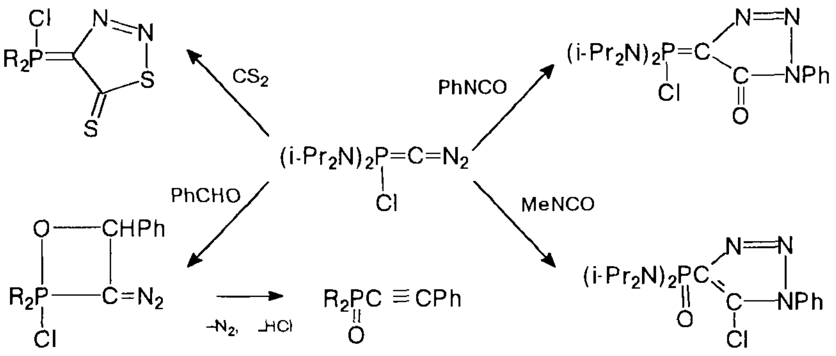
It has been established that the reaction of P-chloro ylides with CO_2 proceeds via the formation of carboxylic acid chlorides; these were isolated in a pure state and were then converted into phosphorus-containing ketenes (Eq.5.121)[140]:



$$\text{t-Bu(Et}_2\text{N)}\underset{\text{Cl}}{\text{P}}\text{=CHPr-i} \xrightarrow{\text{CO}_2} \text{t-Bu(Et}_2\text{N)}\underset{\text{O}}{\overset{}{\text{P}}}\text{CH(Pr-i)COCl} \xrightarrow[-\text{HCl}]{} \text{t-Bu(Et}_2\text{N)}\underset{\text{O}}{\text{P}}\text{C(Pr-i)=C=O} \qquad (5.121)$$

Phosphorus-containing heterocumulenes are distinguished by high stability during storage and vacuum distillation; this is explained by the steric and electronic influence of the phosphoryl group. Thioketenes, for example, are unchanged after storage for several years.. Phosphorus-containing ketenes and thioketenes are very reactive and enter into a variety of addition and cycloaddition reactions[223].

Phosphacumulene ylides give addition products on the diazo group with isocyanates, the P-chloro ylide being formed with phenyl isocyanate and the triazenophosphonate with methyl isocyanate (Scheme 5.36):

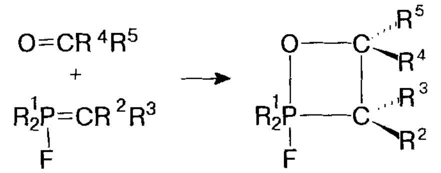


Scheme 5.36

The author supposes that initially nucleophilic attack of the ylide carbon atom on the carbonyl carbon gives a betaine which, depending on the relationship of the oxygen atom (or NR group) to nitrogen or phosphorus, is converted into products of 1,4- and 1,5-cyclization. The unstable 1,4-cycloadduct is transformed initially into an α-diazoimine as a result of a 1,3-halotropic shift and then into the triazenophosphonate[163]. Benzaldehyde gives the 2-chlorooxaphosphetane which readily eliminates hydrogen chloride and is converted into an acetylene phosphonate (Scheme 5.36)[163].

c) Reaction of P-Fluoro Ylides with Carbonyl Compounds

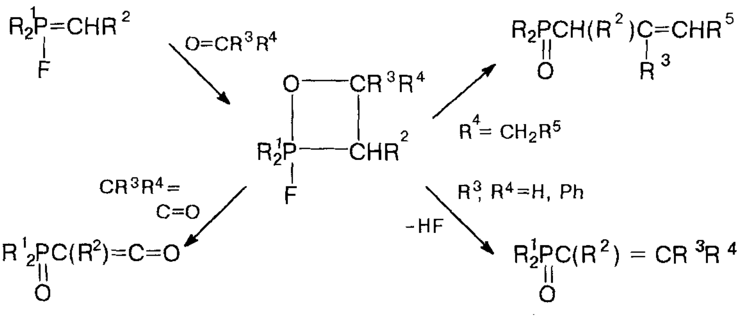
P-Fluoro ylides add carbonyl compounds with the formation of stable 2-fluoro-1,2λ^5-oxaphosphetanes, which are distinguished by their high stability compared with 2-chlorooxaphosphetanes (Eq.5.122). Usually 2-fluorooxaphosphetanes are successfully isolated without difficulty and are purified by vacuum distillation. The stability of 2-fluorooxaphosphetanes is explained by the higher electronegativity of the fluorine atom in comparison with the electronegativities of chlorine and bromine. Consequently the P–F bond of 2-fluorooxaphosphetanes is stable and the compounds do not dissociate with the formation of cyclic phosphonium salts as do 2-chlorooxaphosphetanes[224].



(5.122)

R^1=Alk, Ph; CR^2R^3=CH_2, CHAlk, $CAlk_2$, CHPh, $CHSiMe_3$, CCl_2, CBr_2
CR^4R^5 = C=O, CNPh, CHAlk, $CAlk_2$, CHPh, CPh_2, $CH_2CH{=}CH_2$

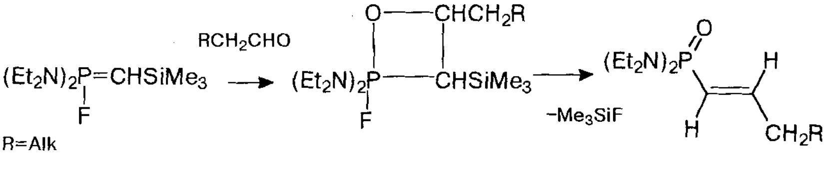
Various stable products of [2+2]-cycloaddition of 2-fluoroylides with alkyl and aryl isocyanates, alkyl and aryl ketones, carbon dioxide, and isocyanates have been synthesized and characterized (Eq.5.122)[224,225]:The reaction of P-fluoroylides with aldehydes and ketones is stereoselective and gives predominantly *threo* diasteroisomers of 2-fluorooxaphosphetanes[74,80], the structure of which was demonstrated by spectroscopic methods (Scheme 5.37)[166,224-226]:



Scheme 5.37

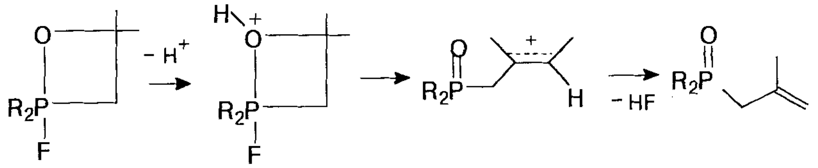
The content of *erythro* diastereomers did not exceed 5–10%. On heating, 2-fluorooxaphosphetanes are, depending on their structures, converted into allyl- or vinylphosphine oxides

The decomposition of 2-fluorooxaphosphetanes usually proceeds with a 1,4-elimination of hydrogen fluoride to afford isomers of allylphosphonates containing the maximum number of alkyl groups on the C=C. The conversion of silicon-containing 2-fluorooxaphosphetanes proceeds with 1,2-elimination of Me_3SiF to furnish stereochemically pure *E*-vinylphosphonates in very good yield (Eq.5.123)[166,226]:



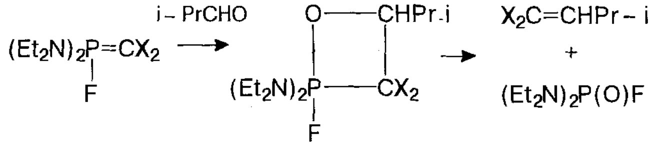
(5.123)

Lewis and Brönsted acids actively catalyze the conversion of 2-fluorooxaphosphetanes into allylphosphine oxides. The reaction is autocatalytic because the hydrogen fluoride eliminated catalyzes the transition of 2-fluorooxaphosphetanes into allyl-phosphine oxides. The decomposition of protonated 2-fluorooxaphosphetanes leads to the formation of oxonium salts; carbenium intermediates occur under conditions of E_N1 elimination to give rise to allylphosphonates (Eq.5.124). The formation of carbenium intermediates was proved by chemical reaction[166,226].



(5.124)

P-Halogenylides react with carbonyl compounds, usually with the formation of phosphorus-containing alkenes. There is a single exception. 2-Fluorooxaphosphetanes, containing chlorine or bromine atoms at C_3, decompose on heating with the formation of 1,1-dihaloalkenes and fluorophosphonates. It is suggested that the electronegative halogen atoms favor transfer of the CX_2 group to an axial position as a result of which the phosphorus-carbon bond is broken and an anion is formed (Eq.5.125)[165,166,202]:

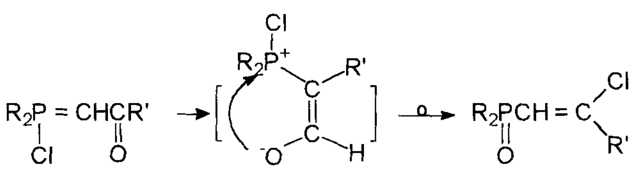


(5.125)

X=Cl, Br

5.3.3.3 Conversions of P-Halogenated Ylides Containing C=O Groups on the α-Carbon

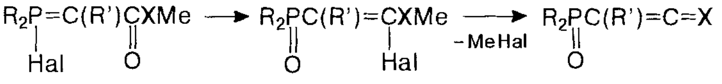
P-Chloroylides with an acyl group at the *α* carbon rearrange upon heating to give *β*-chlorovinylphosphine oxides. The rearrangements proceed via intramolecular attack of the negatively charged oxygen atom on the positively charged phosphorus atom (Eq.5.126)[227]:



(5.126)

R=t-Bu, Alk2N; R'=Alk

P-Halogenated ylides containing an alkoxycarbonyl group on the *α* carbon furnish phosphorylated ketenes at room temperature or on gentle heating[141,143,228]. P-Bromo ylides with a dimethylaminocarbonyl group on the *α* carbon eliminate methyl bromide on heating to 100°C, producing phosphorus-containing keteneimines in good yield (Eq.5.127)[227]:



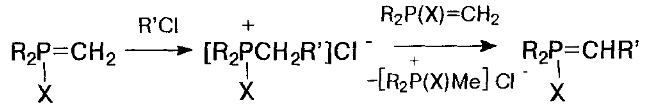
$$R_2\underset{\underset{Hal}{|}}{P}{=}C(R')\underset{\underset{O}{\|}}{C}XMe \longrightarrow R_2\underset{\underset{O}{\|}}{P}C(R'){=}\underset{\underset{Hal}{|}}{C}XMe \xrightarrow[-MeHal]{} R_2\underset{\underset{O}{\|}}{P}C(R'){=}C{=}X \qquad (5.127)$$

X=O, NMe; R=Alk, AlkO, Alk2N; R'=Ph, CO2Me

5.3.3.4 Reactions of P-Chloroylides with Electrophiles

The P=C bond of P-halogenated ylides is strongly polarized as a result of which a significant negative charge is centered on the carbon atom. Consequently P-halogenated ylides readily add various electrophiles with the formation of the corresponding phosphonium salts or betaines.

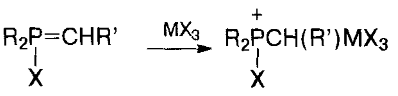
Phosphonium salts formed by reaction of P-halogenylides with such electrophiles as chlorotrimethylsilane, chloroformates, or carboxylic and phosphoric acid chlorides and having an electron-accepting substituent R′ at the α carbon are readily dehydrochlorinated by the initial P-Halogenylide, to furnish C-substituted P-halogenylides (Eq.5.128)[112,134,173]. Phosphonium salts formed by reaction of P-halogenylides with alkyl halides do not, however, enter into transylidation reactions because the alkyl group reduces the lability of the hydrogen atoms at the α carbon[106,183,232].



$$R_2\underset{\underset{X}{|}}{P}{=}CH_2 \xrightarrow{R'Cl} [R_2\overset{+}{\underset{\underset{X}{|}}{P}}CH_2R']Cl^- \xrightarrow[-[R_2P(X)Me]Cl^-]{R_2P(X)=CH_2} R_2\underset{\underset{X}{|}}{P}{=}CHR' \qquad (5.128)$$

X=Br, Cl; R=Alk, Alk2N; R'=Me3Si, R2P, EtOCO, RC(O)

P-Halogenated ylides usually add Lewis acids (boron trifluoride, aluminum chloride) with the formation of betaines (Eq.5.129)[34]. Occasionally, however, reaction of P-chloro ylides with Lewis acids gives phosphinium cations (Eq.5.111)[209]. The reaction of P-chloro ylides with gaseous chlorine leads to the formation of phosphonium salts (Eq.5.130)[187]:



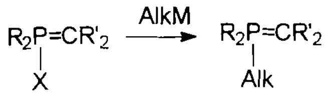
$$R_2\underset{\underset{X}{|}}{P}{=}CHR' \xrightarrow{MX_3} R_2\overset{+}{\underset{\underset{X}{|}}{P}}CH(R')\overset{-}{M}X_3 \qquad (5.129)$$

$$(R_2N)_2P(Cl){=}CCl_2 \xrightarrow{Cl_2} [(R_2N)_2\overset{+}{P}(Cl)CCl_3]Cl^- \qquad (5.130)$$

5.3.3.5 Reactions of P-Halogenated Ylides with Nucleophiles

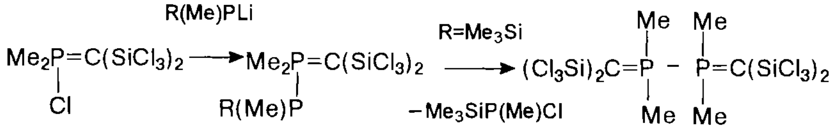
a) Nucleophilic Replacement of the Halogen Atom

The mobile halogen atom of P-halogenated ylides, located on the electrophilic, positively charged phosphorus atom, is capable of ready replacement by various groups on interaction with nucleophiles. Preparatively these reactions are very simple and open wide possibilities for the synthesis of ylides containing almost any substituent at phosphorus. P-Chloro- and P-bromoylides react smoothly with lithium and magnesium alkyls in organic solvents below 0°C to form P-alkyl-substituted phosphorus ylides in good yield (Eq.5.131)[6,119,136,227]:



$$\underset{X}{R_2P}{=}CR'_2 \xrightarrow{AlkM} \underset{Alk}{R_2P}{=}CR'_2 \qquad (5.131)$$

The reaction of P-chloro ylides **126** with lithium phosphides proceeds readily. P-chloro ylides containing trichlorosilyl groups on the α carbon selectively exchange the chlorine atom on the phosphorus for a dimethylphosphine group on interaction with lithium dimethylphosphide. In addition, during reaction of the ylide with lithium trimethylsilylmethylphosphide, the P–P-ylide formed reacts readily with a second molecule of P–Cl ylide and is converted into a double ylide with a P–P bond **127** (Eq.5.132)[230,230a]:

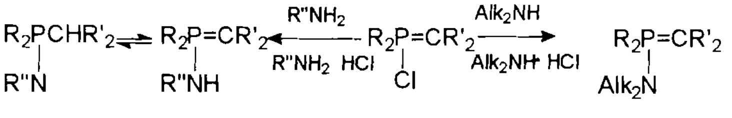


$$\underset{Cl}{Me_2P}{=}C(SiCl_3)_2 \xrightarrow{R(Me)PLi} \underset{R(Me)P}{Me_2P}{=}C(SiCl_3)_2 \xrightarrow[-Me_3SiP(Me)Cl]{R=Me_3Si} (Cl_3Si)_2C{=}\overset{Me}{\underset{Me}{P}} - \overset{Me}{\underset{Me}{P}}{=}C(SiCl_3)_2 \qquad (5.132)$$

126 **127**

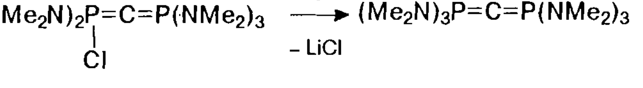
R=Me, Me$_3$Si

P-Chloro ylides react with primary and secondary alkylamines, ammonia, or aniline to provide P–N ylides (Eq.5.133). P-Ylides with a hydrogen atom on nitrogen exist as prototropic tautomeric mixtures with the corresponding iminophosphoranes [9,13,109,112,113,145].



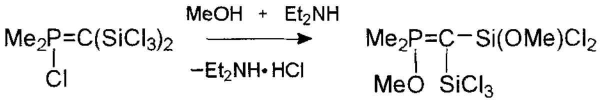
$$\underset{R''N}{R_2P}CHR'_2 \rightleftharpoons \underset{R''NH}{R_2P}{=}CR'_2 \xleftarrow[R''NH_2\ HCl]{R''NH_2} \underset{Cl}{R_2P}{=}CR'_2 \xrightarrow[Alk_2NH\ HCl]{Alk_2NH} \underset{Alk_2N}{R_2P}{=}CR'_2 \qquad (5.133)$$

Symmetrically substituted hexa(dimethylamino)carbodiphosphorane was obtained in high yield by reaction of P-chlorocarbodiphosphorane with lithium dimethylamide in toluene at 20°C (Eq.5.134)[183,232]:

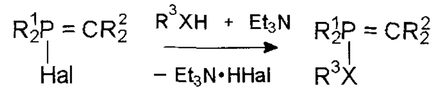


$$(Me_2N)_2\underset{Cl}{P}{=}C{=}P(NMe_2)_3 \xrightarrow[-\ LiCl]{Me_2NLi} (Me_2N)_3P{=}C{=}P(NMe_2)_3 \qquad (5.134)$$

The mobile halogen atoms of P-chloro or P-bromoylides are replaced by alkoxyl, phenoxyl, or thioalkyl groups on reaction with alcohols, phenols, or mercaptans in the presence of triethylamine, giving rise to various types of P-substituted phosphorus ylide (Eq.5.135,136)[9,10,13,119]:



$$\underset{\displaystyle Cl}{Me_2P}=C(SiCl_3)_2 \xrightarrow[-Et_2NH\cdot HCl]{MeOH\ +\ Et_2NH} Me_2\underset{\displaystyle MeO}{P}=\underset{\displaystyle SiCl_3}{C}-Si(OMe)Cl_2 \qquad (5.135)$$



$$R^1_2\underset{\displaystyle Hal}{P}=CR^2_2 \xrightarrow[-\ Et_3N\cdot HHal]{R^3XH\ +\ Et_3N} R^1_2\underset{\displaystyle R^3X}{P}=CR^2_2 \qquad (5.136)$$

R^1=Alk, Ph, AlkO; CR^2_2=$CHCO_2Me$, $C(CO_2Me)_2$, $C(SO_2Ph)_2$
R^3=Alk, Ph; Hal=Br, Cl; X=O, S

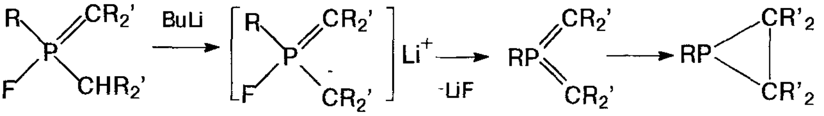
The hydrolysis of P-halogenated ylides proceeds extremely readily to afford, usually, the corresponding phosphine oxides in quantitative yields. The hydrolysis can be used to prove the structure of P-halogenated ylides[10,13,163,167,195].

It has been reported[177] that difluorotriisopropylphosphorane reacts with butyllithium with the formation of butylidenetriisopropylphosphorane (Eq.5.137). The reaction of P-fluoroylides with butyllithium gives a compound of trivalent phosphorus only (Eq.5.138)[189]:

$$i\text{-}Pr_3PF_2 + BuLi \rightarrow i\text{-}Pr_2P(F)=CMe_2 \rightarrow i\text{-}Pr_2P(Bu)=CMe_2 \xrightarrow{BuLi} i\text{-}Pr_3P=CHPr \qquad (5.137)$$

$$(Me_2N)_2P(F)=CH_2 + BuLi \longrightarrow (Me_2N)_2PCH_2Li \qquad (5.138)$$

P-Fluoroylides **128** with secondary alkyl groups on the phosphorus are readily dehydrofluorinated with organolithium compounds. Apparently the organolithium compound metallates the α carbon atom, leading to bis(alkylidene)phosphorane. In the absence of sterically hindered substituents stabilizing the multiple P=C bond, bis(alkylidene)phosphorane cyclizes with the formation of phosphiranes **129** (Eq.5.139)[179]. Dehydrofluorination of P,P-difluoroylides **127** with lithium dihydropropylamide proceeds smoothly and results in fluorophosphiranes **129**, R = F, as a stable liquid distillable under vacuum. The ^{31}P NMR spectra of compounds **129** contain signals δ_P at high fields, doublets with $^1J_{PF}$ 1100 Hz. Fluorophosphiranes having different substituents R and R′ occur as mixtures of *syn* and *ante* isomers.



(5.139)

128 **129**

R=F, Alk2N, Alk

Sec-Butyldifluorophosphonium 2-butylide **128** (Eq.5.139)[179,180d]

a) Bis(*sec*-butyl)phosphine (0.1 mol) was placed in a one-necked round-bottomed Pyrex flask (100 mL) and antimony trifluoride was added by small portions. The reaction mixture was stirred at 80°C for 4 h and then the very dark reaction mixture was cooled to room temperature and the trifluorophosphorane was extracted with diethyl ether. The solvent was removed under reduced pressure and the residue was distilled under vacuum to provide bis(*sec*-butyl)trifluorophosphorane in 70% yield, bp 58–60°C (10 mm Hg).

b) A solution of lithium bis(diisopropyl)amide (0.023 mol) in ether–hexane (~1:1) was added dropwise to a solution of bis(*sec*-butyl)trifluorophosphorane **14** (0.02 mol) in diethyl ether (15 mL) at –60°C. The reaction mixture was then warmed to room temperature and stirred for 10 min at this temperature and then at +35°C. The reaction mixture was filtered, the solvent was evaporated under reduced pressure, and the residue was distilled under vacuum. Yield 80%, bp 50–52°C (10 mm Hg).

2,3-Dimethyl-2,3-diethyl-1-fluorophosphirane **129** (Eq.5.139)

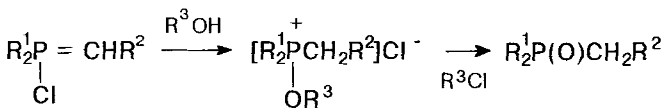
A solution of butyllithium (0.072 mol, 2.1 N) in hexane was added dropwise to a solution of bis(*sec*-butyl)trifluorophosphorane (0.03 mol) in diethyl ether (10 mL) at –60°C The reaction mixture was stirred for 15 min at this temperature and then warmed to +20°C, left for 1 h, and filtered. The solvent was removed under reduced pressure and the residue was distilled under vacuum. Yield 88%, bp 35–40°C (15 mm Hg).

b) Addition Reactions

Reaction of P-chloro ylides with nucleophiles containing a mobile hydrogen atom often results in the formation of addition products to the P=C bond.

P-Chloro ylides add alcohols in ether or pentane below 0°C and are converted quantitatively into unstable alkoxyphosphonium salts which can be isolated as colorless crystalline substances or viscous liquids insoluble in non-polar solvents. On heating alkoxyphosphonium salts were converted into phosphine oxides and on reaction with aqueous sodium perchlorate solution gave stable alkoxy-phosphonium perchlorates[160,231].

Phosphonium salts differing in structure were obtained by reaction of P-chloro ylides with hydrogen halides, hydrazoic acid, ketoenols, and CH-acids. Yield of phosphonium salts are very high and the reaction can, therefore, serve as a preparative method (Eq.5.140)[134,135,231].

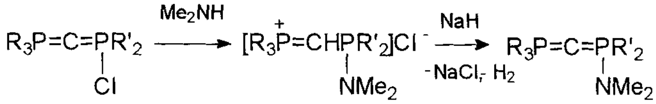


$$\underset{\displaystyle Cl}{R^1_2P} = CHR^2 \xrightarrow{R^3OH} [R^1_2\overset{+}{\underset{\displaystyle OR^3}{P}}CH_2R^2]Cl^- \xrightarrow[R^3Cl]{} R^1_2P(O)CH_2R^2 \qquad (5.140)$$

Ethoxybutyl-di-tert-butylphosphonium chloride

A solution of ethyl alcohol (0.022 mol) in ether (5 mL) was added to a solution of di-*tert*-butyl chlorophosphonium methylide (0.02 mol) in ether (15 mL) at 20°C. The colorless precipitate was removed by filtration, washed with ether, and dried under vacuum. Yield 90%, mp 70°C.

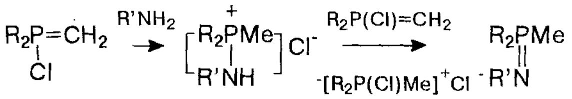
P-Chloroylides add alkyl- and dialkylamines with the formation of aminophosphonium salts. Phosphonium salts containing a dialkylamino group can be converted into P-substituted phosphorus ylides by action of butyllithium or sodium hydride (Eq.5.141)[9,145,183,230]:



$$\underset{\substack{|\\ Cl}}{R_3P{=}C{=}PR'_2} \xrightarrow{Me_2NH} [R_3\overset{+}{P}{=}CH\underset{\substack{|\\ NMe_2}}{P}R'_2]Cl^- \xrightarrow[-NaCl,\ H_2]{NaH} R_3P{=}C{=}\underset{\substack{|\\ NMe_2}}{P}R'_2 \tag{5.141}$$

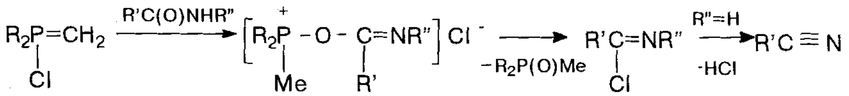
R=Me2N, Et2N, Ph; R'=Me2N, Et2N

Phosphonium salts, formed by reaction of P-chloro ylides with primary alkylamines or aniline, are dehydrochlorinated by excess P-chloro ylide to produce iminophosphoranes. The reaction of P-chloro ylides with amides of sulfonic and phosphoric acids also leads to the formation of iminophosphoranes (Eq.5.142)[230]:



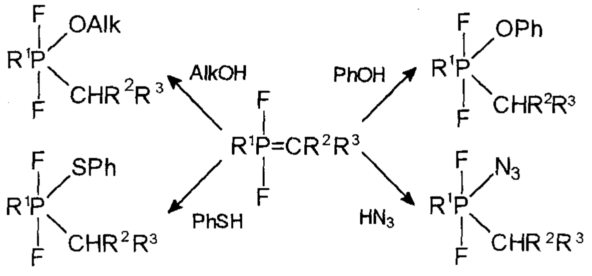
$$\underset{\substack{|\\ Cl}}{R_2P}{=}CH_2 \xrightarrow{R'NH_2} \left[\underset{\substack{|\\ R'NH}}{R_2\overset{+}{P}Me}\right]Cl^- \xrightarrow[-[R_2P(Cl)Me]^+Cl^-]{R_2P(Cl){=}CH_2} \underset{\substack{\|\\ R'N}}{R_2PMe} \tag{5.142}$$

The reaction of P-chloro ylides with carboxylic acid amides proceeds via the formation of an O-phosphorylated intermediate as a result of which imidoyl chlorides are formed. Compounds having substituents R' = Ph_2CH or R" = H are readily dehydrochlorinated by the initial P-chloro ylides to ketenimines or nitriles. In this case P-chloro ylides behave as dehydrating agents (Eq.5.143)[232,233,234,235]:



$$\underset{\substack{|\\ Cl}}{R_2P}{=}CH_2 \xrightarrow{R'C(O)NHR''} \left[\underset{\substack{|\\ Me}}{R_2\overset{+}{P}}-O-\underset{\substack{|\\ R'}}{C}{=}NR''\right]Cl^- \xrightarrow[-R_2P(O)Me]{} R'\underset{\substack{|\\ Cl}}{C}{=}NR'' \xrightarrow[-HCl]{R''=H} R'C{\equiv}N \tag{5.143}$$

P,P-Difluoroylides, which have a highly polar P=C bond, readily add nucleophiles with a mobile hydrogen atom and are converted into difluorophosphoranes in quantitative yields. The reaction of P,P-difluoroylides with alcohols, phenols, and thiophenols proceeds readily in ether or benzene below 0°C to afford almost quantitative yields of difluorophosphoranes (Scheme 5.38)[236,237]::

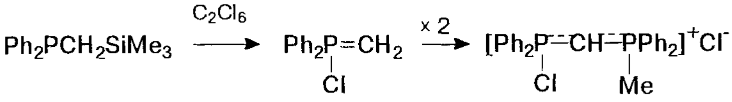


Scheme 5.38

Ethoxy-tert-butylisobutyldifluorophosphorane (Scheme 5.38)[236]
Ethanol (0.02 mol) was added of to a solution of *tert*-butylisobutyldifluorophosphonium isobutylide (Table 5.6; 0.02 mol) in ether (10 mL) at –60°C. Then the temperature was increased to +20°C, the solvent was removed under reduced pressure, and the residue was distilled under vacuum. Yield 80%, bp 67°C (12 mm Hg).

Miscellaneous

One example of the dimerization of P-chloro ylides with the formation of acyclic products was described by Appel and coworkers (Eq.5.144)[167]:



$$Ph_2PCH_2SiMe_3 \xrightarrow{C_2Cl_6} Ph_2\underset{Cl}{P}{=}CH_2 \xrightarrow{\times 2} [Ph_2\underset{Cl}{P}{=}CH{=}\underset{Me}{P}Ph_2]^+Cl^- \qquad (5.144)$$

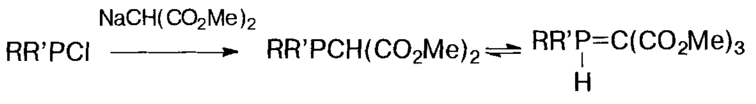
Such are the main achievements in the P-Halogenylide chemistry. It can be concluded that P-Halogenylides are accessible and highly reactive organophosphorus compounds able to take part in various conversions.

5.4 Ylides with a P–H Bond

Alkylphosphines containing an α hydrogen atom can be regarded as carbon analogs of tervalent phosphorus OH acids. Almost all known OH acids of tervalent phosphorus exist in the tetracoordinate prototropic P(O)H form[239]; this can be explained by the high energy of formation of the P=O bond (E_p = 140 kcal mol^{-1}). On the other hand, most alkylphosphines exist in the tricoordinate CH form owing to the inadequate thermodynamic stability of the PH ylide form (Eq.5.145):

$$\begin{array}{l} R_2PCHR'_2 \rightleftarrows R_2P(H){=}CR'_2 \\ R_2POH \rightleftarrows R_2P(O)H. \end{array} \qquad (5.145)$$

The P–H ylide form can be stabilized by two alkoxycarbonyl groups on the α carbon atom as a consequence of the effective delocalization of the negative charge of the ylide carbon atom over the conjugated bond system (Eq.5.146). Thus, dialkyl-bis(methoxycarbonyl)methylphosphines **130** isomerize completely or partly to ylides with a P–H bond **131** (Table 5.11.)[7,24]:



$$RR'PCl \xrightarrow{NaCH(CO_2Me)_2} RR'PCH(CO_2Me)_2 \rightleftharpoons RR'\underset{H}{P}{=}C(CO_2Me)_3 \qquad (5.146)$$

130 **131**

Table 5.11. Tautomer proportions of the dialkyl-bis(methoxycarbonyl) methylphosphines (Eq.146, $CHCl_3$, +20°C)[7]

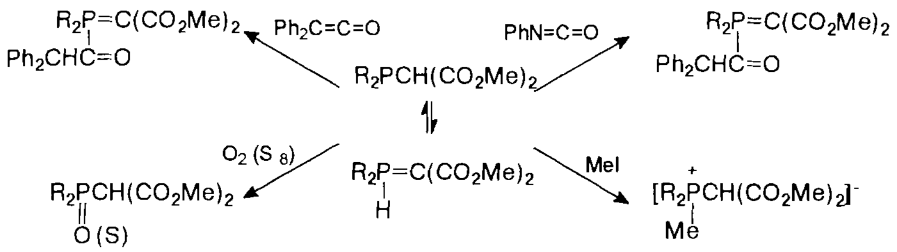
R	R'	**130** (%)	**131** (%)
t-Bu	i-Pr	39	81
t-Bu	s-Bu	35	65
t-Bu	Me_3SiCH_2	10	90
t-Bu	i-Bu	67	33
t-Bu	n-Bu	65	35
n-Bu	n-Bu	85	15
i-Bu	i-Pr	70	30
t-Bu	Me_2N	100	0
t-Bu	Et_2N	100	0

sec-Butyl-tert-butyl-bis(methoxycarbonyl)methylphosphines **130** (Eq.5.146)
A solution of dimethyl malonate (0.35 mol) in THF was added dropwise at 0°C to sodium hydride (0.23 mol) in a 500-mL, three-necked flask equipped with a mechanical stirrer, a pressure-equalizing funnel, and a reflux condenser. The reaction mixture was stirred for 30 min at this temperature, then for 30 min at room temperature, and subsequently was heated under reflux for another 15 min. A solution of *sec*-butyl-*tert*-butylchlorophosphine (0.22 mol) was added to the thus prepared solution of sodium malonic ester at 10°C, and the mixture was then stirred for 2 h at room temperature. The precipitate of sodium chloride was separated by centrifugation, the filtrate was evaporated under reduced pressure, and the residue was distilled under vacuum. Bis(methoxycarbonyl)methyl(*sec*-butyl)*tert*-butylphosphine was isolated as a viscous oil which crystallizes after a few days forming large yellowish crystals. Yield 42.55 g (70%), mp 59°C, bp 95°C (0.08 mm Hg). NMR ($CDCl_3$): δ_H 4.50 (d, $^2J_{HP}$ 2 Hz, PC*H*, form A); 6.50 (d, $^2J_{HP}$ 460 Hz, P*H*, form). δ_P 35.50 (s, form A), 40.00 (d, $^2J_{HP}$ 460 Hz, form B).

It has been demonstrated by spectroscopic studies that dialkylbis(methoxycarbonyl) methylphosphines **130** exist in solution as tautomeric mixtures of the prototropic forms (A) and (B),. The tautomeric equilibrium (A) $\rightleftharpoons$ (B) depends on the temperature, the nature of the solvents, and the substituents on the phosphorus atom. Thermodynamic study of the tautomeric equilibrium led to the conclusion that the ylide form has a higher formation energy than the phosphine form.

The results presented in the Table 5.9 show that bulky and branched alkyl substituents stabilize the PH ylide form and displace the tautomeric equilibrium towards this form; this form is more favorable for the tetracoordinate PH ylide form because the latter is sterically less hindered than the tricoordinate CH form[7,24,240].

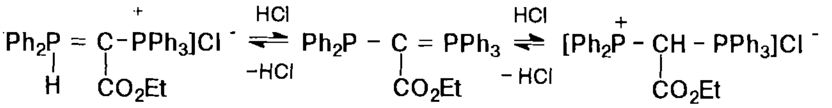
The chemical properties of ylides with a P–H bond are similar to those of other tervalent phosphorus CH acids as a consequence of the involvement of the tricoordinate form in the tautomeric equilibrium[3,7,24]. They are oxidized, add sulfur, and are alkylated by alkyl halides, with the formation of phosphine oxides, phosphine sulfides, and phosphonium salts. Dialkylbis(methoxycarbonyl)methylphosphines readily enter into oxidative ylidation reactions.



Scheme 5.39

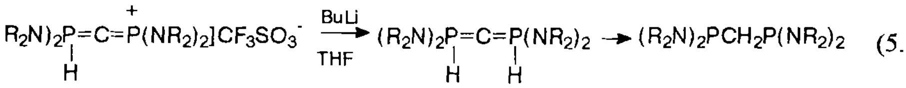
Reaction with phenyl isocyanate or diphenylketene yields P-substituted ylides and reaction with sodium hydride produces phosphino carbanions. Reaction of α-phosphino carbanions with methyl iodide occurs at the phosphorus atom with the formation of the ylide (the 'ylide variant' of the Michaelis–Becker reaction) (Scheme 5.39) [3,7,24].

Detailed studies of the protonation of phosphinophosphonium ylides established that the compound reacts with excess hydrogen chloride in dichloromethane at −80°C with formation of the PH and CH forms of the compounds, and between which equilibrium is established (Eq.5.147)[242–245]:

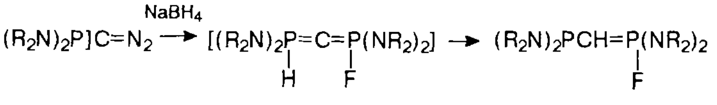


$$\underset{H}{\mathrm{Ph_2\overset{+}{P}}} = \underset{CO_2Et}{\mathrm{C}}\mathrm{-PPh_3]Cl^-} \underset{-HCl}{\overset{HCl}{\rightleftharpoons}} \mathrm{Ph_2P} - \underset{CO_2Et}{\mathrm{C}} = \mathrm{PPh_3} \underset{-HCl}{\overset{HCl}{\rightleftharpoons}} \mathrm{[Ph_2\overset{+}{P}} - \underset{CO_2Et}{\mathrm{CH}} \mathrm{- PPh_3]Cl^-} \qquad (5.147)$$

Bertrand and coworkers reported that ylides with a PH group were readily converted to alkylphosphine oxides (Eq.5.148,149)[247,248]:

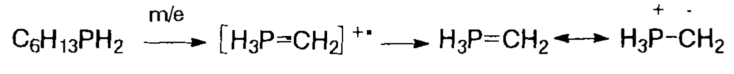


$$\mathrm{R_2N)_2}\underset{H}{\mathrm{\overset{+}{P}}}\mathrm{=C=P(NR_2)_2]CF_3SO_3^-} \xrightarrow[THF]{BuLi} \mathrm{(R_2N)_2}\underset{H}{\mathrm{P}}\mathrm{=C=}\underset{H}{\mathrm{P}}\mathrm{(NR_2)_2} \rightarrow \mathrm{(R_2N)_2PCH_2P(NR_2)_2} \qquad (5.148)$$



$$\mathrm{(R_2N)_2P]C=N_2} \xrightarrow{NaBH_4} \mathrm{[(R_2N)_2}\underset{H}{\mathrm{P}}\mathrm{=C=}\underset{F}{\mathrm{P}}\mathrm{(NR_2)_2]} \rightarrow \mathrm{(R_2N)_2PCH=}\underset{F}{\mathrm{P}}\mathrm{(NR_2)_2} \qquad (5.149)$$

The simplest phosphorus ylide $H_3P=CH_2$ is the most studied hypothetical molecule in organophosphorus chemistry. It has been generated in the gas phase from the radical cation by neutralization–reduction mass spectroscopy and the results support many earlier theoretical predictions about the stability of $H_3P=CH_2$ and the energy barrier (~220 kJ mol^{-1}) to its conversion to the more stable isomeric methylphosphine (Eq.5.150)[246]:



$$\mathrm{C_6H_{13}PH_2} \xrightarrow{m/e} \mathrm{[H_3P=CH_2]^{+\bullet}} \longrightarrow \mathrm{H_3P=CH_2} \longleftrightarrow \mathrm{H_3\overset{+}{P}-\overset{-}{C}H_2} \qquad (5.150)$$

5.5 P-Element-Substituted Phosphorus Ylides

Ylides with a phosphorus–element bond such as P-B, P-Si, P–P, P–As, P–Sb, etc., are the least studied types of the phosphorus ylide, presumably because of the low stability of these compounds. P-element-substituted ylides of phosphorus are readily hydrolyzed, and rearrange into other types of organophosphorus compound, with destructive cleavage of the phosphorus–element bond. At the present time P-element-substituted ylides of phosphorus are of theoretical significance only.

5.5.1 Synthetic Methods

Tervalent phosphorus compounds with a mobile hydrogen atom on the α carbon atom have a distinct tendency to be converted into phosphorus ylides. Thus compounds **132**, $CR'_2{=}C(CO_2Me)_2$, $C(CO_2Me)_2$, and $CHSO_2CF_3$, disproportionate on heating with the formation of ylides **133** containing a phosphorus–phosphorus bond[6,249]. The disproportionation of compounds is a reversible process. On heating with the simultaneous removal from the reaction medium of the non-phosphorylated component $CH_2R'_2$, the equilibrium is fully shifts towards the P–P ylides. This lability is because of effective stabilization by the electron-accepting substituents R′, formed on dissociation of the P–C bond of the carbanion CHR'_2, which becomes capable of playing the role of a readily eliminated group (Eq.5.151)[6]:

$$\underset{\mathbf{132}}{2Et_2PCHR'_2} \xrightarrow{120^\circ\ C} \underset{\mathbf{133}}{Et_2P-PEt_2{=}CR'_2} + CH_2R_2 \qquad (5.151)$$

$CR'_2{=}CHSO_2CF_3,\ C(CO_2Me)_2,\ C(CO_2Et)_2$

The structure of the P–P ylides **133** was confirmed by spectroscopic data. The ^{31}P NMR spectra of these ylides contain a double doublet of signals arising from the tricoordinate and tetracoordinate phosphorus atoms. The constant $^1J_{PP}$ = 270–280 Hz corresponds to the spin–spin coupling of the phosphorus nuclei in the tetracoordinate phosphorus–tricoordinate phosphorus bond.

Tervalent phosphorus compounds containing a mobile hydrogen atom on the α carbon atoms react with chloroalkylphosphines in the presence of triethylamine to result in P–P ylides (Eq.5.152)[6,14,250]. The reaction is performed in ether at 0–10°C:

$$Et_2PCHR'_2 + Et_2PCl \xrightarrow[-Et_3N\cdot HCl]{Et_3N} Et_2P-PEt_2{=}CR'_2 \qquad (5.152)$$

A convenient method for the synthesis of P–P ylides involves the reaction of malonic ester or trifluoromethanesulfonylmethane with two equivalents of chlorodiethylphosphine in the presence of an excess triethylamine[6,249]. The same P–P ylides can be prepared in high yield by reaction of the trialkylphosphines with a mobile hydrogen atom on the α-carbon with chloroalkylphosphines in the presence of triethylamine (Eq.5.153)[6,14,250]:

$$CH_2R_2 + Et_2PCl \xrightarrow{Et_3N} Et_2PCHR_2 \xrightarrow{Et_2PCl\ +\ Et_3N} Et_2PPEt_2{=}CR_2 \qquad (5.153)$$

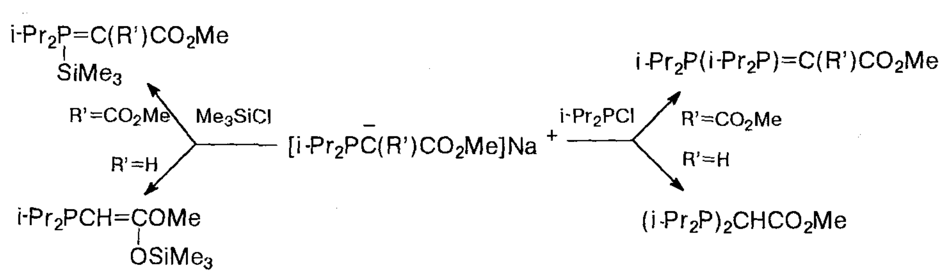
$CH_2R_2{=}MeSO_2CF_2,\ CH_2(CO_2Et)_2$

The α-phosphino carbanions obtained by deprotonation of alkylphosphines by various bases (lithium alkyls[14,251], sodium bis(trimethylsilyl)amide[252], sodium hydride[253], and even alkylamines[254]) can be converted in many instances into P-heterosubstituted phosphorus ylides (Eq.5.154):

$$R_2PCHR'_2 \xrightarrow{M-X} [R_2\overset{-}{P}CHR'_2]M^+ \xrightarrow{R_2PCl} R_2P-PR_2{=}CR_2 \qquad (5.154)$$

$M\text{-}X{=}NaH,\ AlkLi,\ LiN(NSiMe_3)_2;\ R{=}Me,\ Et,\ i\text{-}Pr;$
$CR'_2{=}CHSO_2CF_3.C(CO_2Me)_2,\ C(PMe_2)_2$

The course of the reaction of ambident α-phosphino carbanions with chlorine-containing electrophiles (alkyl halides, tervalent phosphorus chlorides, sulfene chlorides, and chloro-trimethylsilane) is determined by kinetic and thermodynamic factors and depends primarily on the structure of the initial reactants (Scheme 5.40). The presence of electron-accepting groups CO_2R, SO_2R, and Me_2P on the α carbon atom stabilizes the ylide functional group. favoring the formation of products substituted at the phosphorus atom—ylides with P–P, P–S, and P–Si bonds[6,14,253,256]. Thus the carbanion, containing two methoxycarbonyl groups, reacts with *iso*-Pr_2PCl and Me_3SiCl to form the ylides[47] whereas the carbanion with a single methoxycarbonyl group gives rise only to products substituted at the C and O atoms[52]. The stabilization of the P-substitution products by only one MeO_2C group is insufficient in the latter instance[253,257].

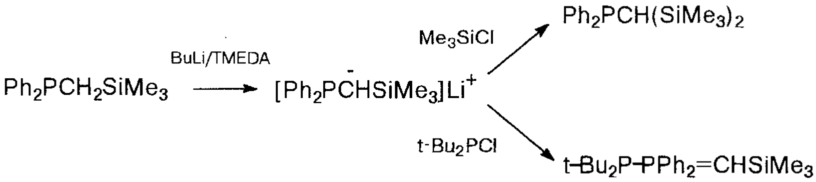


Scheme 5.40

The reaction of bis(diphenylphosphino)methyllithium with chlorodialkylphosphines at −78°C affords P–P ylides which are unstable when the temperature is increased to 20°C and rearrange to triphosphinomethane (Eq.5.155)[254]:

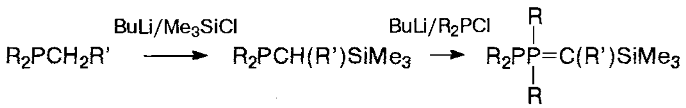
$$[Ph_2P\overset{-}{C}HPPh_2]Li^+ \xrightarrow{R_2PCl} R_2P(PPh_2){=}CHPPh_2 \rightarrow R_2PCH(PPh_2)_2 \qquad (5.155)$$

Diphenylphosphinetrimethylsilylmethyllithium reacts with trimethylsilylchloride to afford the product of C-replacement, bis(trimethylsilyl)methylphosphine, whereas reaction with di-*tert*-butylchlorophosphine results in the P–P ylide (Scheme 5.41)[258]:



Scheme 5.41

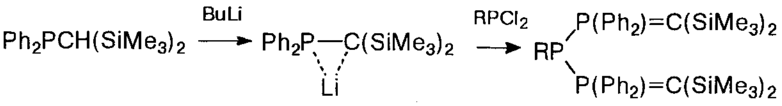
Phosphonic and phosphinic acid amides are lithiated by butyllithium in the presence of tetramethylethylendiamine to form phosphine carbanions; these which react with silyl chlorides to afford C-silyl-substituted products and are phosphorylated with chlorophosphines to give rise to P–P ylides (Eq.5.156)[259]:



$$R_2PCH_2R' \xrightarrow{BuLi/Me_3SiCl} R_2PCH(R')SiMe_3 \xrightarrow{BuLi/R_2PCl} R_2P\underset{R}{\overset{R}{P}}{=}C(R')SiMe_3 \qquad (5.156)$$

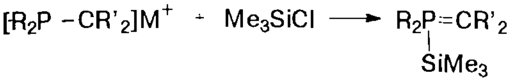
R=Me2N; R'= Ph, SiMe3

The reaction of α-phosphino carbanions with dichlorophosphines leads to the formation of bis-ylides containing P–P–P bond (Eq.5.157)[258]:



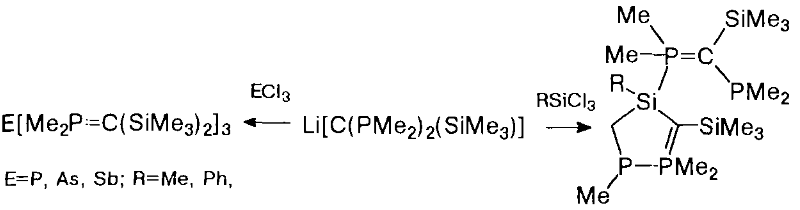
(5.157)

α-Phosphino carbanions bearing electron-acceptor substituents, react with chlorotrimethyl-silane to afford ylides with phosphorus–silicon bonds (Eq.5.158)[3,6,252]. The structure of these ylides was proved by spectroscopic studies and chemical reactions (Table 5.12). Ylides stabilized by alkoxycarbonyl groups are liquids which are distillable in vacuo; ylide bearing sulfonyl groups are crystalline substances[3,6,261]. Karsh et al. reported the synthesis of new P-ylides bearing Si–P, P–P, As–P and Sb–P bonds (Eq.5.159)[263-265]:



$$[R_2P-CR'_2]M^+ + Me_3SiCl \longrightarrow R_2\underset{SiMe_3}{\underset{|}{P}}=CR'_2 \qquad (5.158)$$

R=i-Pr, Ph; R'=CO2Me, SO2Ph; M=Na, MgCl

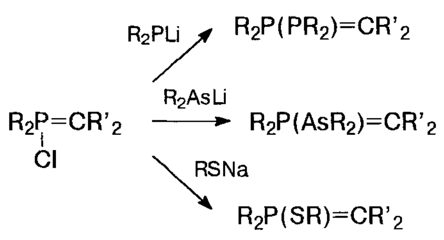


(5.159)

Table 5.12. P-Elementsubstituted Ylides $R^1R^2P(X)=CR^3R^4$

R^1	R^2	R^3	R^4	X	Ref
Et	Et	CO_2Et	CO_2Et	Et_2P	249,250
Et	Et	SO_2CF_3	H	Et_2P	9
i-Pr	i-Pr	CO_2Me	CO_2Me	$i\text{-}Pr_2P$	253
Ph	Ph	Ph_2P	H	$t\text{-}Bu_2P$	255
Ph	Ph	Ph_2P	H	Me_2P	254
Ph	Ph	Ph_2P	H	$(C_6H_{11})_2P$	254
Me	Ph	Ph_2P	H	$t\text{-}Bu_2P$	254
Ph	Ph	Ph_2P	H	Ph_2P	254
Me	Me	Ph_2P	H	$t\text{-}Bu_2P$	254
Me	Me	Me_3Si	Me_3Si	Me_2P	119
Me	Me	Me_3Si	Me_3Si	$Me(Me_3Si)P$	121
Me	Me	$ClMe_2Si$	$ClMe_2Si$	Me_2P	121
Me	Me	Cl_3Si	Cl_3Si	Me_2P	230a
Me	Me	Cl_3Si	Cl_3Si	$Me(Me_3Si)P$	230a
Me	Me	Cl_3Si	Cl_3Si	$(Me_3Si)_2P$	230a
Ph	Ph	Me_3Si	H	$t\text{-}Bu_2P$	258
Me_2N	Me_2N	Me_3Si	H	$(Me_2N)_2P$	259
i-Pr	i-Pr	CO_2Me	CO_2Me	Me_3Si	253
Ph	Ph	$PhSO_2$	$PhSO_2$	Me_3Si	6
i-PrO	i-PrO	CO_2Et	CO_2Et	EtS	13
EtO	EtO	CO_2Et	CO_2Et	EtS	13

Ylides bearing P–P and P–S bonds have been prepared by reaction of P-halogenylides with alkyl- and dialkylphosphines, and also with mercaptans (Scheme 5.42). Examples of syntheses of P–P, P–As, and P–S ylides by this method are presented in Table 5.12[6,13,121,230a].



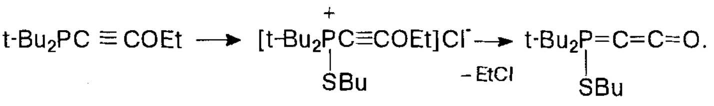
Scheme 5.42

Fritz and Schick reported the synthesis of P–P ylides by reaction of silyldichloromethanes with silylphosphines (Eq.5.160)[121]:

$$(Me_3Si)_2CCl_2 \xrightarrow{Me_3SiPMe_2} (Me_3Si)_2C{=}P(Me)_2PMe_2 \qquad (5.160)$$

Reaction of alkoxyphosphineacetylene with sulfene chlorides proceeds at the phosphorus atom and with elimination of alkyl chloride and leads to the formation of ketenylides containing thioalkyl groups on the phosphorus atom (Eq.5.161,162)[262]:

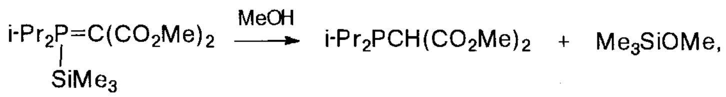
$$[Et_2PC(CO_2Et)_2]^-Na^+ + BuSCl \longrightarrow Et_2P(SBu){=}C(CO_2Et)_2 \qquad (5.161)$$



$$t\text{-}Bu_2PC{\equiv}COEt \longrightarrow [t\text{-}Bu_2\overset{+}{\underset{\displaystyle SBu}{P}}C{\equiv}COEt]Cl^- \xrightarrow[-EtCl]{} t\text{-}Bu_2\underset{\displaystyle SBu}{P}{=}C{=}C{=}O. \qquad (5.162)$$

5.5.2 Properties

Ylides containing P–Si, P–S, and P–P bonds are stable, vacuum-distillable liquids, or crystalline substances. P–P and P–Si ylides are readily cleaved at the phosphorus–element bond by various proton-donating reagents to result in corresponding tertiary phosphines (Eq.5.163–165)[253,256]:



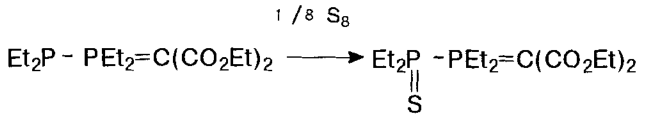
$$i\text{-}Pr_2\underset{\displaystyle SiMe_3}{P}{=}C(CO_2Me)_2 \xrightarrow{MeOH} i\text{-}Pr_2PCH(CO_2Me)_2 + Me_3SiOMe, \qquad (5.163)$$

$$Ph_2PCH{=}P(Ph)_2PR'_2 \xrightarrow{H_2O} Ph_2PCH_2PPh_2 + R'_2P(O)H \qquad (5.164)$$

$$Et_2PPEt_2{=}C(CO_2Me)_2 \xrightarrow{MX} Et_2PCH(CO_2Me)_2 + Et_2PX \qquad (5.165)$$

X=Cl, MeO, HO

P–P ylides are readily oxidized by atmospheric oxygen. The ylides add sulfur to the tervalent phosphorus atom producing new ylides containing the P(S)–P bond (Eq. 5.166)[6,249]:



$$\mathrm{Et_2P-PEt_2{=}C(CO_2Et)_2 \xrightarrow{1/8\ S_8} Et_2\underset{\underset{S}{\|}}{P}-PEt_2{=}C(CO_2Et)_2} \qquad (5.166)$$

When P–P ylides are not stabilized by strong electron-withdrawing or sterically hindered substituents, they rearrange readily to triphosphinomethanes as a result of the migration of the phosphino group to the α carbon atom.(Eq. 5.155)[262].

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6 The Wittig Reaction

$$\boxed{\begin{array}{ccc} R_3P{=}CR'_2 & & R'_2C{=}CR''_2 \\ + & \longrightarrow & + \\ O{=}CR''_2 & & R_3P{=}O \end{array}}$$

6.1. Introduction

The Wittig reaction was born in 1919–1921, when Staudinger and coworkers observed the formation of compounds **1,2** containing C=C bonds during the reaction of the triphenylphosphonium diphenylmethylide with phenyl isocyanate or diphenylketene (Eq. 6.1; 6.2)[1,2]:

$$Ph_3P{=}CPh_2 + Ph_2C{=}C{=}O \xrightarrow[-Ph_3PO]{} \underset{\mathbf{1}}{Ph_2C{=}C{=}CPh_2} \tag{6.1}$$

$$Ph_3P{=}CPh_2 + PhN{=}C{=}O \xrightarrow[-Ph_3PO]{} \underset{\mathbf{2}}{Ph_2C{=}C{=}NPh} \tag{6.2}$$

Staudinger and his students were the first to discover the reaction of ylides with carbonyl compounds which was subsequently named the Wittig reaction. Evidently H. Staudinger was the physical father of this reaction, which was discovered for the second time thirty years later.

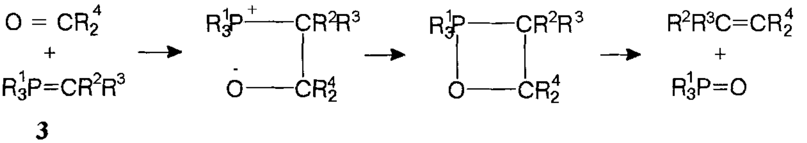
In 1953 Wittig and Geissler treated methyltriphenylphosphonium iodide with phenyllithium and obtained triphenylphosphonium methylide which reacted with benzophenone to afford triphenylphosphine oxide and 1,1-diphenylethylene in 84% yield (Eq. 6.3)[3]:

$$\overset{+}{[Ph_3PMe]}\,Br^- \xrightarrow{PhLi} Ph_3P{=}CH_2 \xrightarrow{Ph_2CO} Ph_2C{=}CH_2 + Ph_3PO \tag{6.3}$$

In his subsequent investigations Wittig[4,5] developed the reaction as a versatile synthetic tool for olefination of carbonyl compounds and applied it to the synthesis of naturally occurring compounds to demonstrate the remarkable advantages of the Wittig reaction for organic synthesis. Therefore, although the reaction was discovered by Staudinger[6–9], the development its synthetic application belongs to Wittig, One of the main virtues of the Wittig reaction, as an important method for the preparation of olefins, is its complete structural specificity, namely, the new carbon–carbon double bond is formed exclusively at the site of the former carbonyl function[7]. The preparation of olefins by other methods, for instance, by dehydration of alcohols, leads to the formation of isomers of the unsaturated compounds[10,11]. A deficiency of the Wittig reaction, especially in the first years after its discovery, was low stereoselectivity, because the reaction led to the formation of mixtures of *Z* and *E* geometric isomers of olefins. However further studies showed that Wittig carbonyl olefination proceeds under effective control for the preferential formation of *Z* or *E* alkenes depending on the desired outcome in a particular circumstance. Such stereocontrol is possible by selection of the type of ylide, the type of carbonyl compound, or the reaction conditions. At present Wittig reactions between phosphorus ylides and aldehydes or ketones are the most important practical method for the construction of carbon–carbon double bonds.

6.1.1 The Wittig Reaction and Related Reactions

The Wittig reaction is the reaction of phosphonium ylides **3** with carbonyl compounds proceeding with the formation of alkenes and phosphine oxides by replacement of carbonyl oxygen with and alkylide group (Eq. 6.4)[12]



3

(6.4)

The first step of the Wittig reaction is in principle the particular case of the general reaction of carbanions with carbonyl compounds, such as the Grignard, Perkow, and Knoevenagel reactions[13]. The essential difference between the Wittig reaction and the above mentioned reactions is the formation of the phosphine oxide by replacement of the carbonyl oxygen; it is this which determines the remarkable chemical properties of phosphorus ylides. Several modifications of the Wittig reaction have been described.

6.1.1.1 Second Staudinger Reaction

The reaction of iminophosphoranes with carbonyl compounds was discovered by Staudinger and coworkers[1,2,14] over 70 years ago (Eq. 6.5)

$$R_3P{=}NR' + R''_2C{=}O \longrightarrow R'N{=}CR''_2 + R_3P{=}O \qquad (6.5)$$

Today this reaction is used so often to create C=N bonds that it is one of the most widely used in organic synthesis[15]. The reaction has been named the Staudinger reaction[16] (or the Second Staudinger reaction, to distinguish it from the First Staudinger reaction—the reaction of tertiary phosphines with azides[16,17]), the name used in the Russian and German literature, and also the Aza–Wittig reaction, the name used by *Chemical Abstracts*. However the first title, unquestionably, is more exact, because Wittig did not study this reaction

6.1.1.2 The Horner–Emmons Reaction

The chemistry of phosphinoxy carbanions began with the discovery by Horner in 1958 that they react with carbonyl compounds to form alkenes and diphenylphosphinates. Horner[18] was the first who recognize that a phosphonate carbanion would react with a carbonyl compound to produce an alkene and a phosphorous acid salt. In subsequent publications Horner developed this reaction (Eq. 6.6; 6.7)[19]:

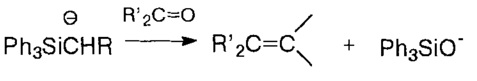
$$Ph_2P(O)Me \xrightarrow{NaNH_2} Ph_2P(O)CH_2^- \xrightarrow{Ph_2C=O} Ph_2C=CH_2 + Ph_2P(O)O^- \qquad (6.6)$$

$$(RO)_2P(O)CH_2Ph \xrightarrow{BuLi} RO)_2P(O)C^-HPh \xrightarrow{Ph_2C=O} Ph_2C=CHPh + (RO)_2P(O)O^- \qquad (6.7)$$

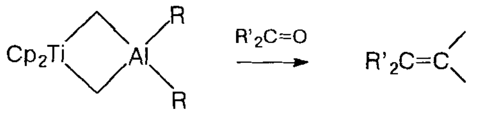
Very soon this reaction was recognized as a useful supplement to the Wittig reaction, and it is, therefore, most often called the Horner–Wittig reaction[16]. Pommer[20] in 1960 and Trippett and Walker[21] in 1961, reported early examples of the application of the Horner–Wittig reaction in organic synthesis. Wadsworth and Emmons (from 1961)[22] studied the Horner–Wittig reaction in detail and developed it into an important synthetic tool applicable to a range of phosphonate and carbonyl compounds. Therefore this procedure discovered by Horner, is called the Horner–Emmons reaction (Horner–Wadsworth–Emmons reaction) and may be regarded as a useful supplement to the Wittig reaction. The Wadsworth–Emmons modification of the Horner–Wittig reaction uses sodium hydride in dimethoxyethane, enabling the reaction to be performed under soft conditions and olefins to be obtained in the highest yields. The carbonyl olefination reaction employing phosphoryl-stabilized carbanions (the Horner–Emmons reaction) is now a well-established and useful alternative to the Wittig olefination. The Horner–Emmons reaction of anions derived from phosphine oxides, phosphonates, phosphonamides, and their thiono counterparts has well-documented advantages in many situations

6.1.1.3 Peterson and Tebbe Reagents

Attempts to modify and to expand the Wittig reaction are well-known. For instance, the Peterson reagent[23], carbanions stabilized by a silicon atom (Eq. 6.8), and Tebbe reagents (Eq. 6.9)[24,25], which are not as widespread as the Wittig and Horner reagents[26], in some cases afford very good results and thus complement the Wittig reaction.



(6.8)



(6.9)

6.2 General Positions

The area of the application of the Wittig reaction is exceedingly broad, because of the possibility of changing the structure of ylide and carbonyl compound. The high selectivity of the Wittig reaction enables the use of carbonyl compounds of different structures bearing different functional groups (ester, alcohol, epoxy, etc.). The conditions used for the Wittig reaction depend on the structures of the ylide and the carbonyl compound; the nature of the solvent, the presence of dissolved additives, the temperature and pressure also affect on the rate and the stereochemistry of the Wittig reaction

6.2.1 The Structure of the Phosphorus Ylide

The activity of phosphorus ylides in the Wittig reaction depends on their structure.[27-32] Substituents on the carbon and phosphorus atoms of the P=C bond affect the activity of the ylide in the Wittig reaction and the stereochemistry of the alkene formation. The greatest effect on the activity of phosphorus ylides in the Wittig reaction is that of carbanion substituents. Depending on the structure of the ylide carbanion the phosphorus ylides can be classified as hyperactive ylides, active ylides (or non-stabilized ylides), ylides of moderate activity (or semistabilized ylides), ylides of low activity (or stabilized ylides), and unreactive ylides (betaines) (Table 6.1).

The most reactive are the Corey–Schlosser **hyperactive** ylides **4**[33a] and the Cristau ylide-carbanions **5**,[33b] which readily undergo the Wittig reaction with aldehydes and ketones.

$Ph_3P{=}CHLi$	$R_2P(CH_2Li){=}CH_2$	$R_3P{=}CR^1R^2$
4	**5**	**6**

Very active also are **non-stabilized** phosphonium ylides of type **6** with electron-donating or electroneutral substituents R^1 and R^2 = H, Alk, AlkO, Alk_2N on the ylide carbanion. These compounds actively undergo the Wittig reaction with aldehydes and with ketones. **Semi-stabilized** ylides of type **6** with moderate electron-withdrawing groups (R^1, R^2 = phenyl, thioalkyl, vinyl groups, halogen atoms and so on) on the α–

carbon atom react actively with aldehydes, although they are less active toward ketones.

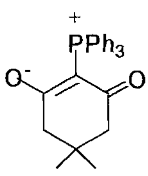
Table 6.1. Approximate reactivities of phosphorus ylides toward carbonyl compounds

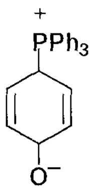
Reactivity	Aldehydes	Ketones
Hyper reactive	+++[a)]	+++
Highly reactive	+++	++
Moderately reactive	++	+
Poorly reactive	+	–
Unreactive	–	–

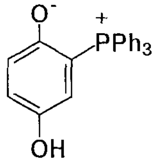
[a)] +++, react very easily; ++, react readily; +, react; –, do not react.

The activity is strongly reduced for **stabilized** ylides of type 6 with strong electron-withdrawing groups (R^1 or R^2 = sulfonyl, alkoxycarbonyl, phosphono, *p*-nitrophenyl groups, etc.) or groups capable of delocalizing the negative charge (cyclopentadienylide, fluorenylide) of the ylidic carbon atom

For instance, triphenylphosphonium cyclopentadienylide does not react with carbonyl compounds even on heating[27]. Triphenylphosphonium fluorenylide reacts with aldehydes only when heated, and does not react with ketones[28]. Triphenylphosphonium carboethoxymethylide reacts comparatively readily with aldehydes, but only sluggishly with ketones[29]. There are structures with pseudoylidic properties:





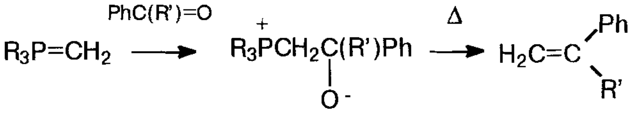


Because of the low contribution of the ylidic structure to the ground state, such highly stabilized ylides do not enter into the Wittig reaction even on prolonged heating—the betaine structure is preferred to the ylide structure[30,31].

Electron-donating substituents on the phosphorus atom increase the electron density on this atom and increase the basicity of ylides[32]. Replacement of the triphenylphosphonium group with tri-*n*-butylphosphonium[32b] or tris(dimethylamino) phosphonium[32a] increases the activity of phosphorus ylides in the Wittig reaction.

Wittig[34] and Trippet and Walker[35,36] reported that ylides containing electrondonating groups (methyl, morpholine, *p*-methoxyphenyl) on the phosphorus atom react with carbonyl compounds to afford stable betaines 7 which are converted to alkenes only on heating (Eq. 6.10):

Electron-acceptor fluorine or chlorine atoms on the phosphorus atom increase the stability of the cyclic adducts in the Wittig reaction (see Chapter 5).[37] Bulky groups on the phosphorus atom seems not to inhibit the reactivity of ylides substantially, but affect the stereochemistry[38]. Introduction to the phosphorus atom of groups restricting

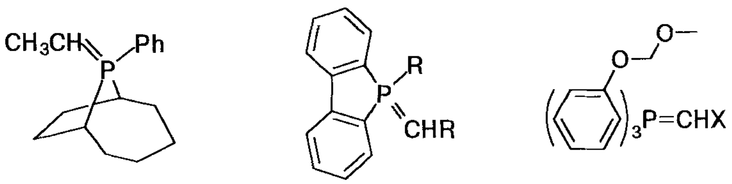


$$R_3P{=}CH_2 \xrightarrow{PhC(R')=O} R_3\overset{+}{P}CH_2\underset{O^-}{C}(R')Ph \xrightarrow{\Delta} H_2C{=}C\begin{matrix}Ph\\R'\end{matrix} \tag{6.10}$$

7

R=Me, 4-C_6H_4OMe, $C(CH_2CH_2)_2N$

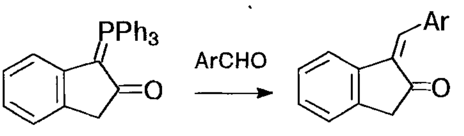
pseudorotation in the transition state, such as a bridgehead bicyclic phosphorus group in **8**, increase the stereoselectivity of the Wittig reaction (*E*:*Z* = 100:1)[38]. The bicyclic ylide **9** reacts readily with aldehydes to afford *E* alkenes with selectivity >94%[39a,6.] The replacement of phenyl groups in triarylphosphonium ylides by 2-methoxymethoxyphenyl groups also increases the stereoselectivity of the Wittig reaction, for instance in the synthesis of 1-alkenylhalides and vinyl ethers from ylides **10.** Usually *Z* selectivity >97% for 1-alkenylhalides, in some cases 99–99.5%; for vinyl esters *Z* selectivity can be >90% (Scheme 6.1)[40]:



8 **9** **10**

Scheme 6.1

Good *Z* stereoselectivity for ylide **11** (Eq. 6.11)[41] and ylide **12** (Eq. 6.12)[42a,b] are observed in the Wittig reaction:



(6.11)

11

$$Ph_3P{=}CHCH_2CO_2^- + RCHO \longrightarrow E\text{-}RCH{=}CHCH_2CO_2H \tag{6.12}$$

12

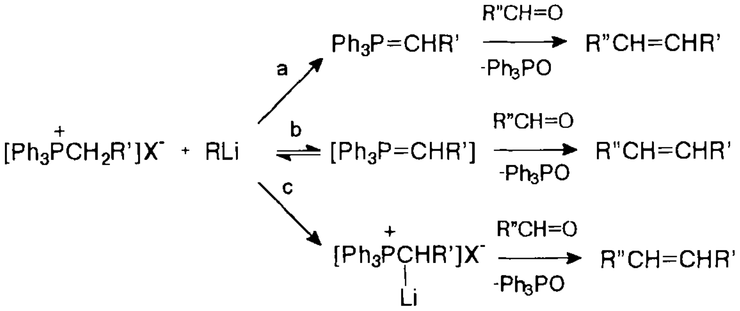
The Wittig reaction can be performed with isolated and purified phosphorus ylide, which undergoes reaction with carbonyl compounds to produce the olefin and phosphine oxide; alternatively a phosphonium salt is used as the starting compound and is treated with an appropriate base:

Three general directions of the Wittig reaction in this case are possible (Scheme 6.2):

(a) The deprotonation of the phosphonium salt leads to the formation of salt-free ylide solution; the ylide can be isolated in the pure state or detected by physical or chemical methods.

(b) The phosphonium salt exists in equilibrium with the phosphorus ylide, which is present in the solution at a minimum concentration and cannot be detected physical methods. It does, however, undergo the Wittig reaction, because of the shift of the equilibrium toward the formation of the olefin.

(c) The phosphonium salt with lithium alkyl gives and organometallic derivative which, although not the phosphorus ylide, olefinates the carbonyl compound analogously to true phosphorus ylides, with the formation of olefin and phosphine oxide. The stereochemical result of this reaction is considerably different for that of the Wittig reaction:

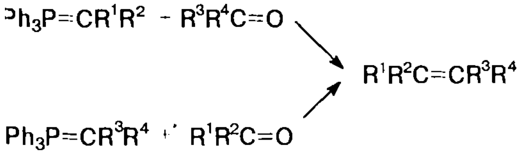


Scheme 6.2

6.2.2 The Structure of the Carbonyl Compound

Phosphorus ylides enter to the Wittig reaction with different carbonyl compounds—aliphatic and aromatic aldehydes, unsaturated aliphatic and arylaliphatic aldehydes, aliphatic and aromatic ketones, various mixed saturated and unsaturated alkylarylketones, thioketones, ketenes, isocyanates, esters, amides, ylides, and anhydrides of carboxylic and carbonic acids.

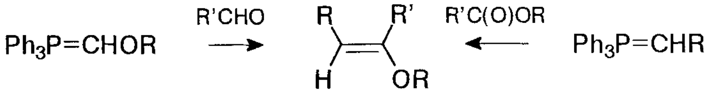
The activity of carbonyl compounds in the Wittig reaction depends on their electrophilicity and decreases in the sequence: ketenes >> aldehydes > ketones > esters ≈ amides.



Scheme 6.3

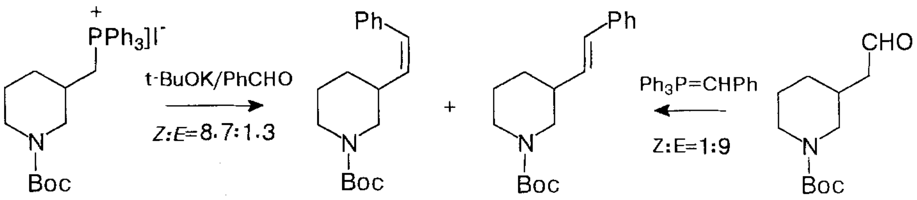
The variation of the structure of carbonyl compounds enables constraints connected with choice of the structure of ylidic component to be overcome, because for the synthesis of any olefin by the Wittig reaction the substituents on the ylidic and the carbonyl carbon atoms can be varied (Scheme 6.3).

For example vinyl esters can be prepared by two ways: from alkoxymethylides and aldehydes and from alkylides and esters as shown in Scheme 6.4.[8]



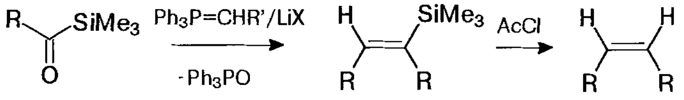
Scheme 6.4

Mantegani et al. developed the stereoselective synthesis of the *E* and *Z* isomers of 3-styrylpiperidines (Scheme 6.5):[437]



Scheme 6.5

Introduction to the carbonyl compound of protecting groups creates interesting synthetic possibilities. Thus, the reaction of non-stabilized ylides with aliphatic derivatives of acylsilanes in the presence of the lithium salts at low temperature gives *Z*-1,2-disubstituted vinylsilanes in very high (>96%) stereoselectivity (Table 6.2). The trimethylsilyl group can be removed by the action of acetyl chloride in acetonitrile, with the formation of stereochemically pure olefins (Eq. 6.13).[43,44]



R=Me, Bu, i-Pr, t-Bu; R'=Me, Pr, i-Pr, OMe

(6.13)

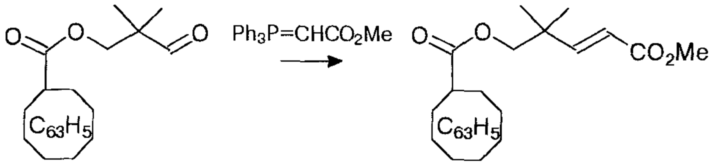
Table 6.2. Z-Vinyl silanes from acylsilane/P-ylide combination (Eq. 6.13)[44]

R	R'	Yield(%)	Z:E
Bu	Pr	41	98:2
Me	Pr	82	96:4
i-Pr	Me	37	98:2
$Cl(CH_2)_4$	Pr	40	98:2
Me	OMe	50	78:22

Analogously acyl stannanes react with various P-ylides to afford the corresponding vinyl stannanes.[45]

6.2.2.1 Aldehydes

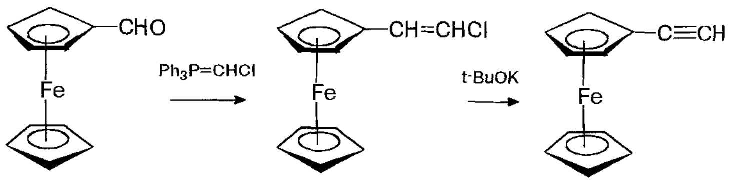
The reaction of phosphorus ylides with aldehydes usually proceeds readily, regioselectively, and with high yields of olefins. Aldehydes of various structure were introduced into the Wittig reaction. Evidently there is no almost limit to the structure of aldehydes which can be used in the Wittig reaction[48–50]. Thus the fullerene olefins were successfully obtained from organofullerenes by the Wittig reaction (Eq. 6.14)[46]:



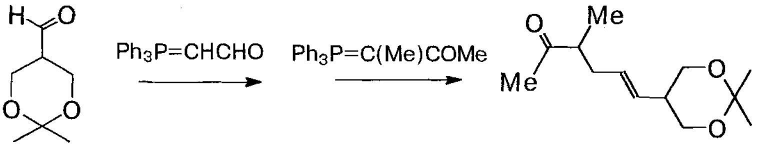
(6.14)

Seleno- and thioaldehydes react smoothly with P-ylides to result in predominantly *E* olefins in 29–69% yield.[47]

The Wittig reaction of formylferrocene with the triphenylphosphonium chloromethylide followed by dehydrohalogenation leads to the formation of the ethynylferrocene.. The latter is used as a synthon for the construction of oligonucleotide organometallic systems (Eq. 6.15)[50.] Diene, a key intermediate in enantioselective synthesis of (–)-cassioside, was prepared by two consecutive Wittig reactions (Eq. 6.16)[52]:



(6.15)

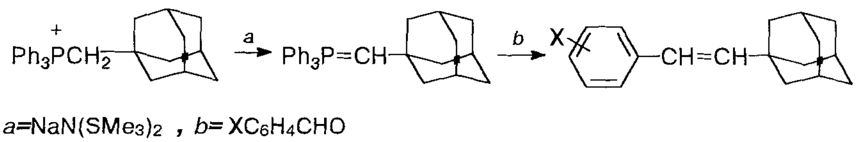


(6.16)

New aldehydes can be prepared by reaction of P-ylides with acetals and thioacetal-protected glyoxal; this enables the length of the carbon chain to be increased (Eq. 6.17)[8,53b]:

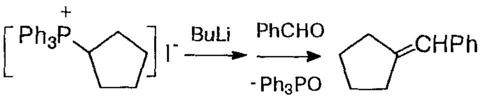
$$Ph_3P{=}CHR + OHCCH(XR)_2 \longrightarrow RCH{=}CH(XR')_2 \longrightarrow RCH{=}CHCHO \qquad (6.17)$$

There are a few reports of the influence of steric obstacles to the carbonyl group on the Wittig reaction[24,53]. Sterically hindered aldehydes react with phosphorus ylides very slowly or do not react. An increase in Z stereoselectivity is usually observed for the sterically hindered carbonyl compounds pivaldehyde[53–55], 17-ketosteroids[56], and methyl isopropyl ketone[57]. Yamataka et al. reported the synthesis of triphenylphosphonium 1-adamantylmethylide.[51] The reaction of this P-ylide with *ortho*-substituted benzaldehyde provides alkenes in 90% *E* stereoselectivity (Eq. 6.18)[51]:

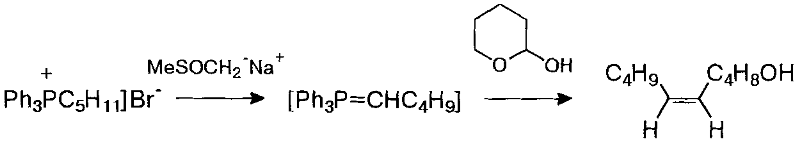


(6.18)

The Wittig reaction with aldehydes depends on the electrophilicity of the C=O group of the aldehydes to a greater extent than that with ketones[58]. Electron-accepting substituents in the *para* position of aromatic aldehydes increase the reactivity toward phosphorus ylides[59–61].



(6.19)



(6.20)

Benzylidenecyclopentane (Eq. 6.19)[62]

A solution of butyllithium (40 mmol) in absolute ether (60 mL) was added to triphenylcyclopentylphosphonium iodide (18.3 g, 40 mmol) under nitrogen. After stirring for 2 h a dark red solution of the triphenylphosphonium cyclopentylide was formed. The mixture was cooled and a solution of benzaldehyde (4.3 g, 40.5 mmol) in absolute ether (10 mL) was added dropwise. The mixture was left for 10 h at 30°C. Then the triphenylphosphine oxide was separated and washed with an aqueous solution of bisulfite (40%, 3 x 20 mL) and with water until neutral. The solution was dried with calcium chloride, the solvent was removed under reduced pressure, and the residue was distilled in vacuo. Yield 4.1 g (85%), bp 123–124°C (20 HPa).

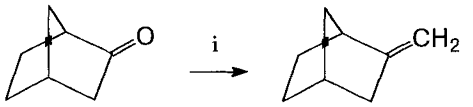
Z-5-Decen-1-ol-1 (Eq. 6.20)[63]

A suspension of sodium hydride (0.05 mol) was placed into the round-bottomed flask and washed with hexane. Then DMSO (25 mL) was added to the sodium hydride and the reaction mixture was slowly heated to 75°C and hydrogen evolution was observed. After cessation of gas evolution the mixture was heated at this temperature for 10–15 min. and then cooled to room temperature to give the deep-red solution of the ylide. A solution of 2-hydroxytetrahydropyran (2.5 g, 11.5 mmol) in dry DMSO (5 mL) was added dropwise and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was then diluted with cooled water and extracted with hexane (3 x 20 mL). The solvent was removed under reduced pressure and the residue was distilled under vacuum. Yield 80%, bp 110–115°C (10 mmHg), *Z*:*E* isomer ratio = 93:7.

The main problem of the Wittig reaction with aldehydes is its comparatively low stereoselectivity. Various modifications and improvements of the Wittig reaction have been developed to increase the stereoselectivity (See Section 6.4).

6.2.2.2 Ketones

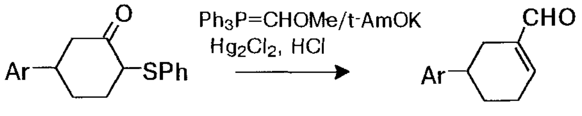
Ketones are less active in the Wittig reaction, than aldehydes[64-70]. Often the Wittig reaction of P-ylides with ketones proceeds only on heating. For instance, triphenylphosphonium methylide undergoes the Wittig reaction with the sterically hindered ketone fenchone only on heating to 120°C in dimethyl sulfoxide. The reaction of fenchone with hyperactive ylides[46,65]proceeds at room temperature (Eq. 6.21). The Tebbe reagent is more active in reactions with ketones than is triphenylphosphonium methylide[24,25].



(6.21)

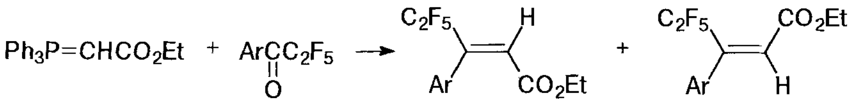
i=$Ph_3P=CHLi$, $Ph_2P(CH_2Li)=CH_2$.

Interesting examples of the Wittig reaction of phosphorus ylides with ketones have been described. For instance, the reaction of methoxymethylide with α–phenylthioketone furnishes 1-formylcyclohexene (Eq. 6.22).[67]



(6.22)

Ketones bearing electron-withdrawing substituents, which increase the electrophilicity of the carbonyl group, are the most active. The Wittig reaction of triphenylphosphonium carboethoxymethylide with fluorinated alkylketones proceeds smoothly under normal conditions to result in fluorinated alkenes of stereoselectively *Z*:*E* = 20:1) (Eq. 6.23)[61,69]:

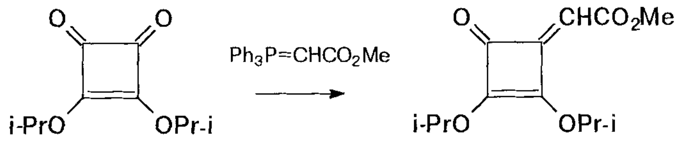


(6.23)

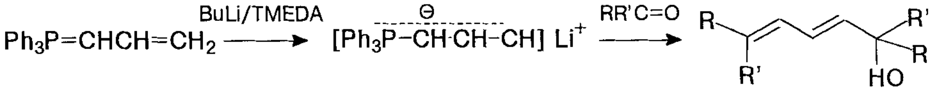
Z: E=20: 1

Olefination of dialkyl squarates by the Wittig reaction results in the corresponding *Z*-olefin derivative in very good yield (Eq. 6.24)[70]:

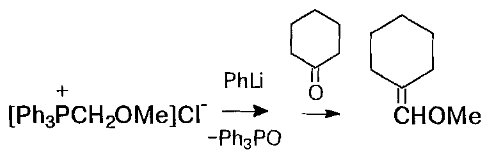
Introduction to the carbonyl compound of protecting groups creates interesting synthetic possibilities. Thus, the reaction of non-stabilized ylides with aliphatic deriva-


(6.24)

Shen and Wang have described a one-pot synthesis of β-hydroxy-1,3-dienes via reaction of the allylic 1,1-ylide-anion with two mole equivalents of carbonyl compound (Eq. 6.25)[70b]:

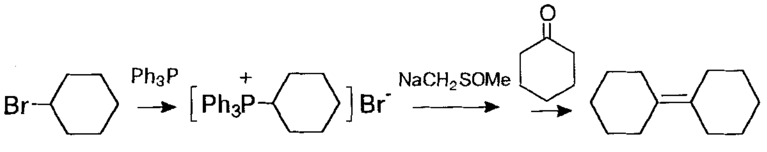

(6.25)

We propose several examples of the olefin preparations by Wittig reaction with ketones


(6.26)

Methoxymethylenecyclohexane (Eq. 6.26)[64]

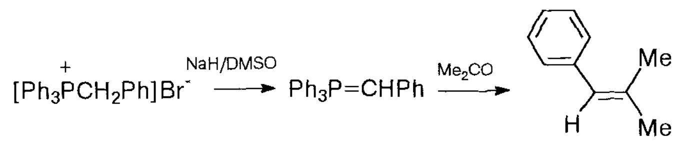
A solution of phenyllithium (60 mmol) in ether was added to a suspension of methoxymethyltriphenylphosphonium chloride (21.25 g, 62 mmol) in absolute ether (200 mL) under argon at room temperature. After 10 min the reaction mixture was cooled to −30°C and a solution of cyclohexanone (5.88 g, 60 mmol) in ether (10 mL) was added dropwise. The mixture was left for 15 h at room temperature and the precipitate of triphenylphosphine oxide was removed by filtration. The filtrate was evaporated and the residue was distilled under reduced pressure, bp 74°C (48 mmHg). Yield 5.4 g (71%).


(6.27)

Dicyclohexylidene (Eq. 6.27)

(a) A mixture of bromocyclohexane (8.1 g, 0.05 mol) and triphenylphosphine (13.1 g, 0.05 mol) was heated under reflux for 1–1.5 h on an oil bath under nitrogen. The reaction mixture was cooled, washed with benzene, and triturated to obtain colorless solid cyclohexylphosphonium bromide. The mixture was removed by filtration and dried. Yield 18–20 g (85–95%).

(b) A solution of dimsyl sodium (0.05 mol) was prepared in dimethyl sulfoxide and added under nitrogen to cyclohexyltriphenylphosphonium bromide (16 g). The mixture was gently heated to complete the reaction, then cyclohexanone (5 mL) was added and the mixture left stirring for 10 min. The reaction mixture was poured into water and extracted with petroleum ether (4 x 25 mL), and the extracts were combined and dried with the sodium sulfate. The solvent was evaporated, the residue was distilled under vacuum, bp 120–130°C (1–2 mmHg), mp 55°C. Yield 4 g (65%).



(6.28)

β,β-Dimethylstyrene (Eq. 6.28)[71]

(a) Benzyl bromide (8.5 g, 0.05 mol) and triphenylphosphine (13.1 g, 0.05 mol) were mixed in a flask. The mixture was heated on water bath until crystallization (~10 min). The mixture was washed with benzene to remove the starting compounds, filtered, and dried.

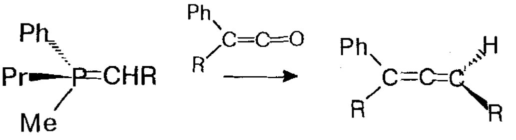
(b) Sodium hydride (2.3 g, 0.05 mol; 50% suspension) was placed in a flask equipped with a reflux condenser. The sodium hydride was washed with dry petroleum ether (bp 40–60°C; 20 mL). Sodium-dried dimethyl sulfoxide (20 mL) was then added and the reaction mixture was stirred until dissolution of the sodium hydride. Triphenylphosphonium bromide (20 g, 0.05 mol) was added to the reaction mixture with stirring. The mixture turned a bright-orange color indicating formation of the ylide. Then acetone (5 mL) was added and the reaction mixture was heated gently until completion of the reaction. The mixture was diluted with water (250 mL) and extracted three times with petrol ether. The extracts were combined, dried with sodium sulfate, and the solvent was evaporated. A few crystals of hydroquinone were added to the residue and it was distilled under vacuum. The fraction corresponding to *β,β*-Dimethylstyrene, bp 60–65°C (1 mmHg) was collected. Yield 4 g (60%).

6.2.2.3 Heterocumulenes

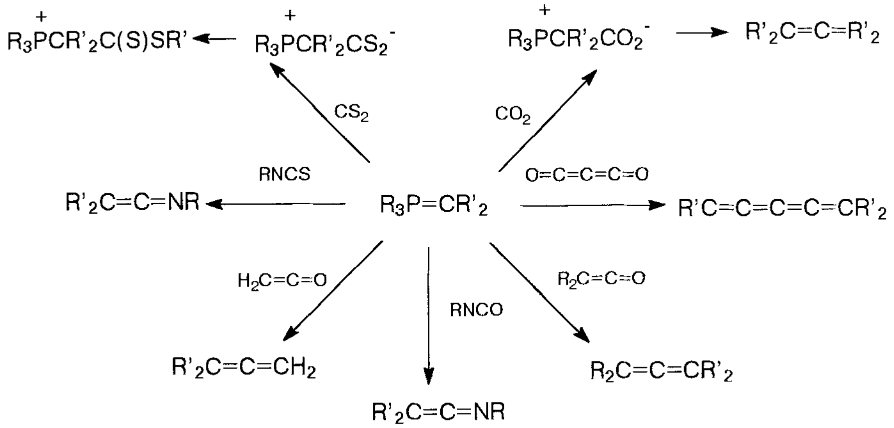
Although the first example of the reaction of phosphorus ylides with ketenes and isocyanates was described by Staudinger 80 years ago[1], only recently has this reaction been intensively studied.[71-89]

The reaction of the phosphorus ylides with heterocumulenes, carbon dioxide[71], carbon suboxide[72-74], carbon disulfide[75,76], isocyanates[77,78], ketenes[58,79], and isothiocyanates [80,81], proceeds with the formation of new heterocumulenes, allenes, and cumulenes. Owing to the high electrophilicity of heterocumulenes the reaction proceeds comparatively readily to furnish high yields of alkenes. (Scheme 6.6).

Thus the reaction between chiral ylides and ketenes results in partial kinetic resolution and with the formation of optically active allenes (Eq. 6.29)[82]:

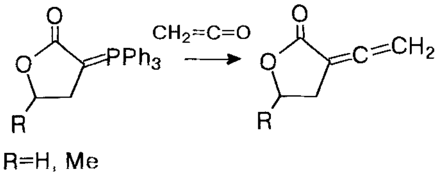


(6.29)



Scheme 6.6

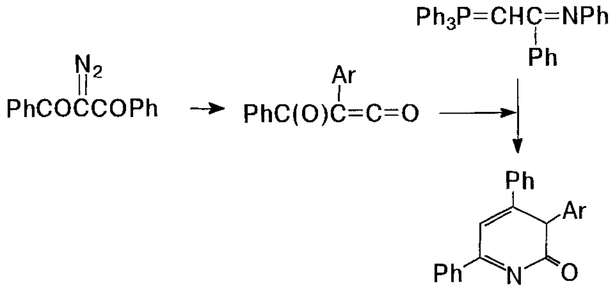
α-Vinylidene γ-butyrolactone, which has notable biological activity was prepared in high yield by the Wittig reaction of ylides with gaseous ketene (Eq. 6.30)[83]:



(6.30)

α-Vinylidene γ-butyrolactone (Eq. 6.30)[83]

Gaseous ketene from acetone pyrolysis is bubbled into a solution of ylide (27 g, 80 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0°C and the reaction is monitored by ^{31}P NMR. When no more ylide is detected the solution is concentrated by one fourth by rotary evaporation. The triphenylphosphine oxide is precipitated with ether–pentane 1:1 (150 mL) and removed by filtration. Concentration and flash chromatography on silica gel with ether afford pure allenic lactone. Yield 7.9 g (90%).



Scheme 6.7

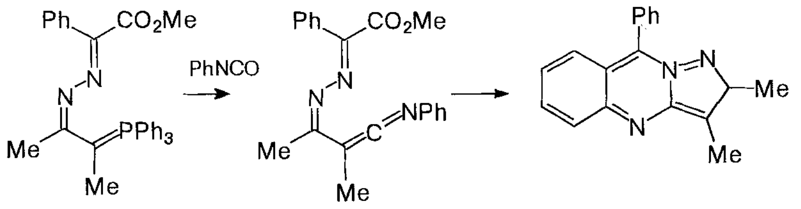
Capuano and coworkers described the synthesis of a number of five- and six-membered monoheteroatom rings by reaction of ylides with α-acylketenes generated by Wolff rearrangement (Scheme 6.7)[84,85]

Nader and Brecht[72,73] and Pandolfo[74] showed that reaction of phosphorus ylides with carbon suboxide proceeds with the formation of cumulenes (Eq. 6.31):

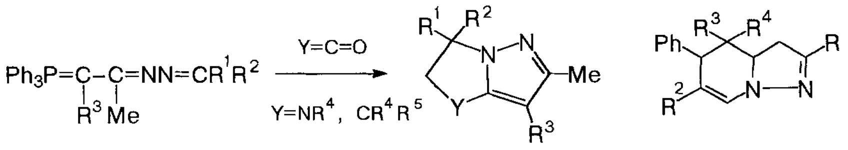
$$Ph_3P{=}C(R)X \xrightarrow{O=C=C=C=O} XC(R){=}C{=}C{=}C{=}C(R)X \qquad (6.31)$$

$X{=}CN,\ CO_2R$

Schweizer and coworkers[86] on the basis of the reaction of phosphorus ylides with isocyanates, ketenes, and carbon disulfide developed a versatile method for the synthesis of 4,5-dihydropyrazol, quinolines, isoquinoline, benzothiazine, and quinazoline derivatives[58,89]. The reaction probably proceeds via the formation of the allene intermediates (Eq. 6.32; 6.33):

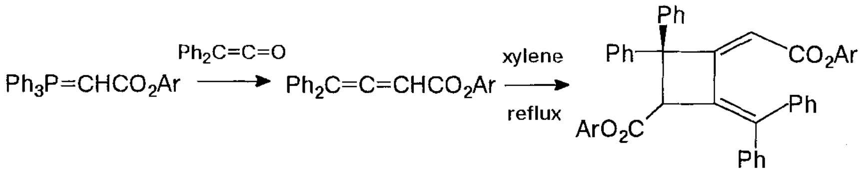


(6.32)



(6.33)

Himbert and Fink realized the cycloaddition of diphenylketene to triphenylphosphonium carboethoxymethylide[88]. Allenecarboxylates, obtained by Wittig reaction, readily cyclize when heated under reflux in xylene, producing cyclobutane derivatives (Eq. 6.34):



(6.34)

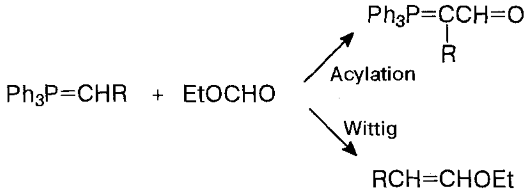
6.2.2.4 Carboxylic Acid Derivatives

Carboxylic acid derivatives (esters, amides, imides, anhydrides) are less active in the Wittig reaction than are aldehydes and ketones. Olefination of carboxylic acid derivatives can be performed only with highly nucleophilic phosphorus ylides or with carbonyl compounds activated by electron-accepting substituents.[90] The great electrophilicity of fluorinated acid derivatives enables P-ylides to add to the carbonyl group of esters[91–93] and even amides[94].

a) Esters

Generally the main limitation of a Wittig reaction with carboxylic acid derivatives is the poor reactivity of non-activated esters, especially amides with alkylidenephosphoranes. The addition of a P-ylides to a carboxylic ester is possible when the ylides are sufficiently reactive or the esters are activated.[90-105]

Non-stabilized P-ylides react with non-activated esters to afford P-acyl ylides, whereas no reaction occurs with stabilized P-ylides[91]. Activated esters react with stabilized P-ylides to provide enol ethers[95]. Depending on the reaction conditions ylides react with esters with the formation of new C-acylated ylides or olefins (See Chapter 2). Le Corre and coworkers showed, that non-stabilized ylides (R= Alk) react with ethyl formate at room temperature with the formation of ketoylides or, at –78°C, of vinyl ethers, in low yield. Reaction of stabilized ylides (R= Ph, CO_2Et) with ethyl formate afford vinyl esters in yields of approximately 90% (Scheme 6.8)[95]:



Scheme 6.8

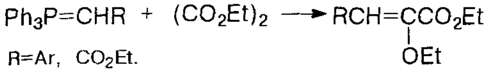
Carbethoxyethenyl ethyl ether (Scheme 6.8)[95]

A mixture of triphenylphosphonium carboethoxymethylide (17.5 g, 0.05 mol) and 40 ml of ethyl formate was heated under reflux for 4 h. The reaction mixture was cooled in ice and the triphenylphosphonium oxide was separated by filtration. Excess ethyl formate was removed by distillation at atmosphere pressure. Distillation of the residual liquid at 0.5 mmHg gave 6.8 g (95%) of a pleasant smelling liquid boiling at 60-61° C.

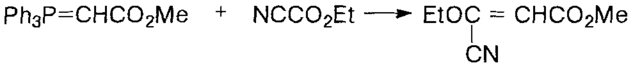
Ethyl styryl ether (Scheme 6.8)[95]

The triphenylphosphonium benzylide was generated from benzyltriphenylphosphonium chloride (39.0 g, 0.1 mol) and sodium hydride (2.6 g, 0.1 mol) in 400 ml of DMSO. Ethyl formate (15 g, 0.2 mol) was added to the benzylide and stirred at room temperature for 3 h. The reaction mixture was thrown into 800 ml of water, the mixture was extracted with pentane and the extract was dried over anhydrous magnesium sulfate. Pentane was distilled off under reduced pressure. A clear colorless liquid boiling at 63°C (1 mm Hg) was obtained in 90% yield (13.3 g).

Cristau lithium-substituted ylide-carbanions react readily with esters to give only C-acylated products[96]. Diethyl oxalate reacts with stabilized ylides to result in vinyl esters in yields of 21–67%, and *Z*:*E* isomer ratio of 6–20:1 The reaction of stabilized phosphorus ylides with ethyl cyanoformate produces cyanovinyl esters in high yields (Eq. 6.35;Eq. 6.36)[97,98]:

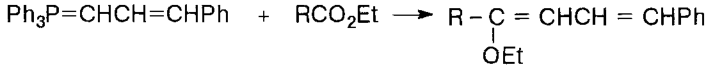


$$\underset{R=Ar,\ CO_2Et.}{Ph_3P{=}CHR} + (CO_2Et)_2 \longrightarrow RCH{=}\underset{OEt}{\underset{|}{C}}CO_2Et \qquad (6.35)$$

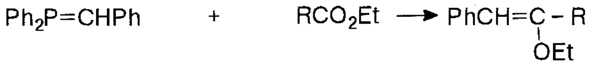


$$Ph_3P{=}CHCO_2Me + NCCO_2Et \longrightarrow EtO\underset{CN}{\underset{|}{C}} = CHCO_2Me \qquad (6.36)$$

Benzylids, and allylphosphonium ylides undergo the Wittig reaction with active esters of carboxylic acids [R = H, CO_2Et, $CH(OEt)_2$]. The Wittig reaction of stabilized phosphorus ylides with ethyl cyanoformate produces cyanovinyl esters in high yields[98]. The highest yields of vinyl esters (67–91%) were obtained when R = H or CO_2Et (Eq. 6.37,38) [98]:



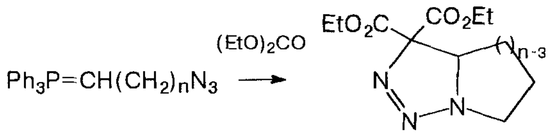
$$Ph_3P{=}CHCH{=}CHPh + RCO_2Et \longrightarrow R-\underset{OEt}{\underset{|}{C}} = CHCH = CHPh \qquad (6.37)$$



$$Ph_2P{=}CHPh + RCO_2Et \longrightarrow PhCH{=}\underset{OEt}{\underset{|}{C}}-R \qquad (6.38)$$

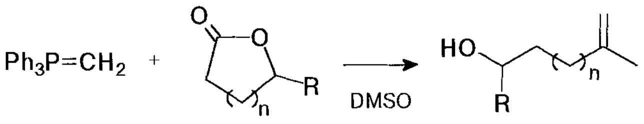
R=H, CO_2Et, $CH(OEt)_2$

The Wittig reaction of P-ylides with diethyl carbonate proceeds with the formation of triazoles (Eq. 6.39)[99]:



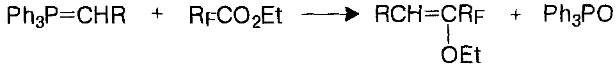
(6.39)

The reaction of P-ylides with lactones leads usually to acyl-ylides or phosphonium carboxylates (See Sect. 2.3.4.2.8). However Brunel and Rousseau reported recently that the reaction of medium-ring lactones with four equivalents of a non-stabilized P-ylide leads to the formation of open-chain alkene derivatives (Eq. 6.40)[105]:



(6.40)

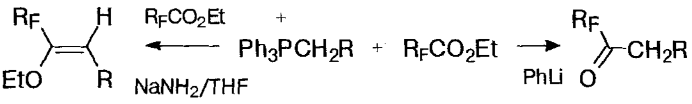
Esters of fluoro-substituted carboxylic acids, especially esters of trifluoroacetic acid which are highly electrophilic because of the electron-accepting trifluoromethyl group, react readily with P-ylides. Yields of isolated and purified vinyl esters were not less than 65–82% (Eq. 6.41)[101]:



$$\mathrm{Ph_3P{=}CHR + R_FCO_2Et \longrightarrow RCH{=}\underset{\underset{OEt}{|}}{C}R_F + Ph_3PO} \qquad (6.41)$$

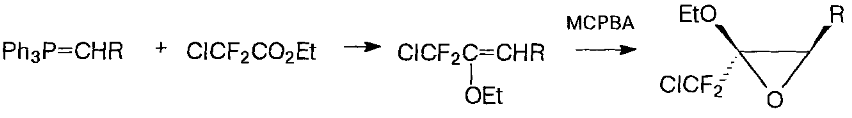
R=Ph, Alk; $R_F=CF_3, CH_2F$

The Wittig reaction was performed using salt free conditions in THF (or benzene) with various perfluoroalkyl ethyl esters ($R_F = CF_3, C_2F_5, C_3F_7, C_7F_{15}, CF_2Cl$) and P-alkylides generated from phosphonium salts with $NaNH_2$ as a base in the presence of catalytic amounts of HMDS (Scheme 6.9). In all cases *Z*-enol esters 8 ($R_F = C_nF_{2n+1}$) were obtained in moderate to good yields (45–75%). The reaction is stereoselective—according to NMR only Z-enol ethers were obtained[91]. They are stable to acidic or basic hydrolysis. The reaction leads to the formation of 1-perfluoroalkylketones in the presence of lithium salts (butyllithium was used as a base)[91]



Scheme 6.9

On the basis of the reaction of α-fluoro-substituted acetic acid esters with P-ylides a method for the synthesis of the fluorine-containing epoxides was developed (Table 6.3, Eq.42)[102]:

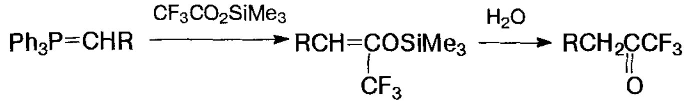


13 **14** (6.42)

Table 6.3. Synthesis of the fluorine-containing epoxides **14** (Eq. 6.42)[102]

R	Yield of **13** (%)	Yield of **14** (%)
Ph	58	80
$CH_2CH(OEt)_2$	42	60
$c\text{-}C_6H_{11}$	50	82

The reaction of silyl esters of trifluoroacetic acid with active ylides when heated under reflux in benzene provides enolsilylic esters in good yields. The hydrolysis of silyl esters furnishes fluorine-containing ketones in 80-95% yields (Table 6.4, Eq.43).[92]

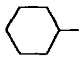
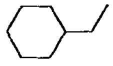
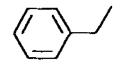
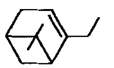


$$\mathrm{Ph_3P{=}CHR} \xrightarrow{\mathrm{CF_3CO_2SiMe_3}} \underset{\mathrm{CF_3}}{\mathrm{RCH{=}COSiMe_3}} \xrightarrow{\mathrm{H_2O}} \underset{\mathrm{O}}{\mathrm{RCH_2CCF_3}} \quad (6.43)$$

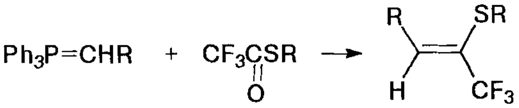
R=Ph, c-C_6H_{11}, C_6H_{13}, $PhCH_2CH_2$ **15** **16**

The preparation of enolsilylated esters 16 (Table 6.4, Eq.6.43)[92]
A phosphonium salt (0.05 mol), sodium amide (0.05 mol), benzene (15 mL), and hexamethyldisilazane (0.001 mol) were placed in a three-necked flask under nitrogen. The mixture was heated under reflux with stirring until the termination of the elimination of ammonia. Then benzene (150 mL) was added and the mixture was left for 30 min for precipitate formation. The solution was transferred into another flask and the trimethylsilyl ester was added dropwise until discoloration of the reaction solution. The solution was then heated under reflux for 1–4 h, the solvent was evaporated, pentane was added, and the triphenylphosphine oxide was removed by filtration. The pentane was evaporated and the residue was fractionated under vacuum.

Table 6.4 The reaction of silyl esters of trifluoroacetic acid with P-ylides (Eq. 6.43)[92]

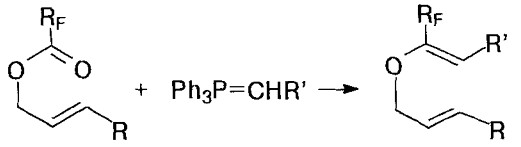
R	Yield of **15** (%)	Yield of **16** (%)
Ph	48	95
C_6H_{13}	40	95
$PhCH_2CH_2$	70	92
	78	95
	50	90
	58	80
	51	90

Thioesters undergo the Wittig reaction with P-ylides. Both stabilized and non-stabilized P-ylides react with S-alkyl trifluorothioacetates to provide trifluoromethylvinylsulfides in yields varying from moderate to high of predominantly the *Z* isomer (Eq. 6.44)[103].



$$\mathrm{Ph_3P{=}CHR} + \underset{\mathrm{O}}{\mathrm{CF_3CSR}} \longrightarrow \mathrm{(R)(H)C{=}C(SR)(CF_3)} \quad (6.44)$$

α-Fluoroalkylenol esters were obtained by the *Z*-selective Wittig reaction of the corresponding perfluoroalkanoates (Eq. 6.45)[105]. The compounds then undergo Clausen rearrangement at 100°C producing the γ,δ-unsaturated perfluoroalkylketones. Fluorinated amides undergo the Wittig reaction with ethoxycarbonylmethylide[106]:

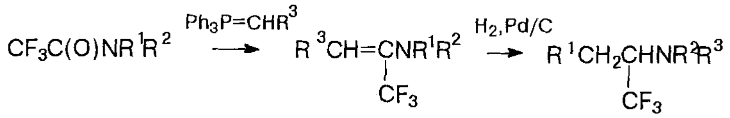


(6.45)

b) Amides

Examples of the Wittig reaction of phosphorus ylides with carboxylic acid amides have been described in the last few years.[106-110]

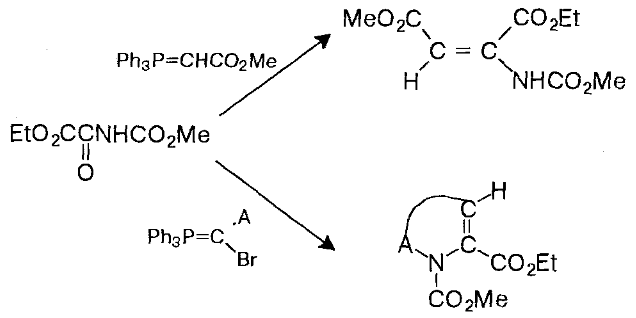
Activated amides bearing electron-accepting trifluoromethyl or alkoxycarbonyl substituents on the *a* carbon atom enter into the Wittig reaction the most easily[106]. Trifluoroacetamides react with non-stabilized and with semi-stabilized ylides when heated under reflux THF or benzene with the formation of 1-trifluoroethyleneamines; these were reduced to 1-trifluoromethylalkylamines. The synthesis has been reported of *Z*:*E* mixtures of trifluoromethylated enamines by condensation of various trifluoroacetamides with P-ylides generated in salt-free conditions by $NaNH_2$ and HMDS (Eq. 6.46)[94]:



$$CF_3C(O)NR^1R^2 \xrightarrow{Ph_3P=CHR^3} R^3CH=\underset{\displaystyle CF_3}{\underset{|}{C}}NR^1R^2 \xrightarrow{H_2,Pd/C} R^1CH_2\underset{\displaystyle CF_3}{\underset{|}{C}}HNR^2R^3 \qquad (6.46)$$

R^1=H, Me, Bz; R^2=H, Bz; R^3=C_6H_{13}, Ph, $Ph(CH_2)_2$, c-$C_6H_{11}CH_2$;
NR_2=pyperidine, morpholine

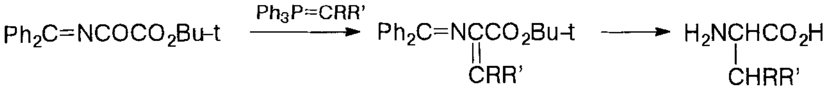
Ethyl-*N*-carbomethoxyoxamate reacts with triphenylphosphonium carbomethoxymethylide with the formation of unsaturated *α*–amino acid derivatives. The reaction of *N*-carbomethoxyoxamate with *ω*-haloalkylides is accompanied by heterocyclization producing cyclic *α*–dehydroaminoesters (Scheme 6.10).[107]



A=$C(O)CH_2$, $(CH_2)_2$, $(CH_2)_3$, 2-$C_6H_4CH_2$

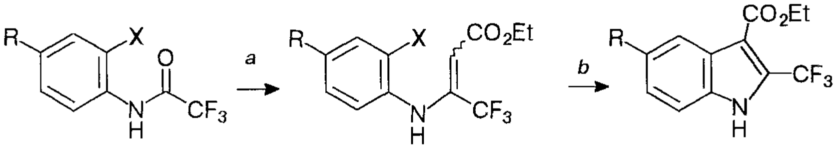
Scheme 6.10

Phosphorus ylides react with tert-butyl *N*-(diphenylmethyl)oxamate to afford 2-aza-1,3-dienes[108], which were reduced by sodium cyanoborohydride to *α*-amino acid derivatives (Eq. 6.47):



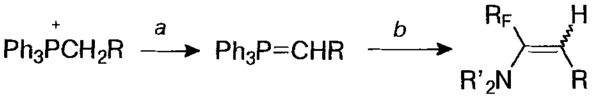
$$\mathrm{Ph_2C{=}NCOCO_2Bu\text{-}t} \xrightarrow{\mathrm{Ph_3P{=}CRR'}} \mathrm{Ph_2C{=}N\underset{\underset{CRR'}{\|}}{C}CO_2Bu\text{-}t} \longrightarrow \mathrm{H_2N\underset{\underset{CHRR'}{|}}{C}HCO_2H} \qquad (6.47)$$

The reaction of P-ylides with perfluoroacetamides leads to the formation of a mixture of the *Z* and *E* isomers of enamines, which under Heck reaction conditions are converted into indoles and quinolones (Eq. 6.48).[91,110] Several enamine, morpholine, piperidine, and dibenzylamine derivatives have been prepared by this way. Hydrolysis of these enamines in acidic medium provides the corresponding fluorinated ketones in quantitative yields (Eq. 6.49):



(6.48)

a= $\mathrm{Ph_3P{=}CHCO_2Et}$; b= $\mathrm{Pd(OAc)_2/PPh_3}$; X= CN, $\mathrm{CO_2Et}$, $\mathrm{NO_2}$



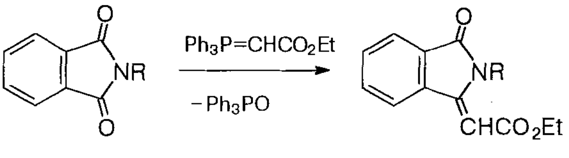
(6.49)

a= $\mathrm{NaNH_2/THF}$, BuLi; *b*= $\mathrm{R_FC(O)NR'_2}$

Amides do not undergo the Wittig reaction with alkylidenephosphoranes. Only perfluoro-alkylamides participate in the Wittig reaction. Reaction time is long (~24 h in boiling THF) and yields are strongly dependent on the nature of the amino residue and on the R_F chain. Yields decrease with increasing steric hindrance and with increasing basicity of the amino group.

c) Imides

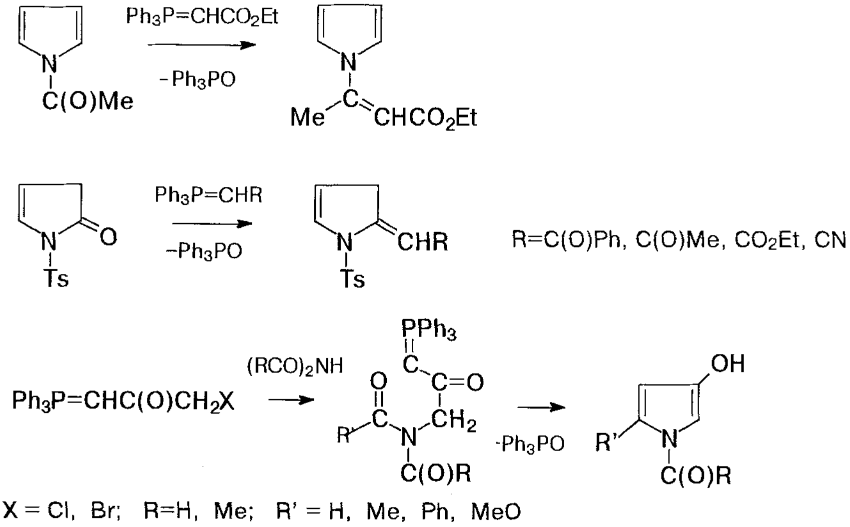
Several examples have been described of the reaction of phosphorus ylides with imides proceeding with the formation of alkenes were described (Scheme 6.11)[111-115]. Phthalic acid imides can be olefinated on one carboxyl group in reasonable yield by reaction with triphenylphosphonium carboethoxymethylide (Eq. 6.50):[111]



(6.50)

R=H,Me

Carboxylic acid imides are of comparatively low activity in the reaction with stabilized phosphorus ylides—the reaction proceeds only when heated to 140–180°C (Eq. 6.51, 6.52). The yields of olefins are 50–80% on average[112–114]. Flitsch,[114,115] by reaction of imides with triphenylphosphonium α-halogenoacetylmethylides, via the step of the formation of N-alkylated phosphorus ylides, obtained N-acyl-3-hydroxypirroles in reasonable yields (Eq. 6.53)


(6.51)

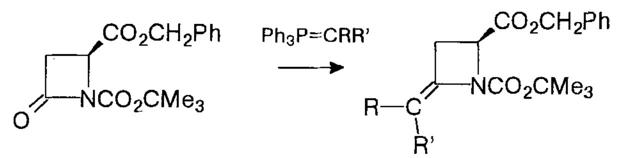
R=C(O)Ph, C(O)Me, CO2Et, CN (6.52)

(6.53)

X = Cl, Br; R=H, Me; R' = H, Me, Ph, MeO

Scheme 6.11

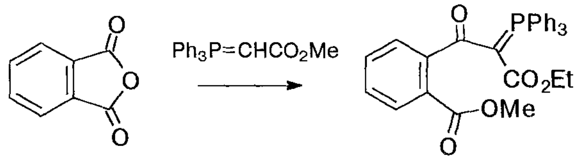
The Wittig reaction was used in the synthesis of β–lactam derivatives.[116-118] Uyeo and Itani used the Wittig reaction for the preparation of 2-functionalized-methyl-1β–methylcarbapenems.[116] Baldwin and co-workers reported that the Wittig reaction of some activated monocyclic β-lactams with stable ylides proceeds with good stereoselectivity and excellent yield (Eq. 6.11)[118]


(6.54)

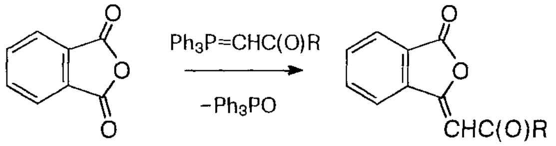
R=H, Me; R'=EtO2C, t-BuO2C;

d) Anhydrides

The Wittig reaction between stabilized phosphorus ylides and cyclic anhydrides leads to the formation of enol-lactones.[119-129] Enol-lactones have a wide range of biological properties from potent antibiotics to sweet-scented components of perfumes, and are therefore intensively studied. Yields of enol-lactones are approximately 60%, the *Z*:*E* isomer ratio depending on the structures of the ylides and the reaction conditions (Eq. 6.55, 6.56).[119-122] The mechanism of the Wittig reaction of P-ylides with cyclic anhydrides was described recently by Kayser[123]. The reaction of alkoxycarbonylmethylides and dialkylamidocarbonylmethylides with phthalic anhydride on heating to 100–120°C affords *E* isomers of lactones; acylmethylides give predominantly *Z* isomers. At 40°C the reaction always led to the formation of the *E* isomer (Table 6.5).



(6.55)



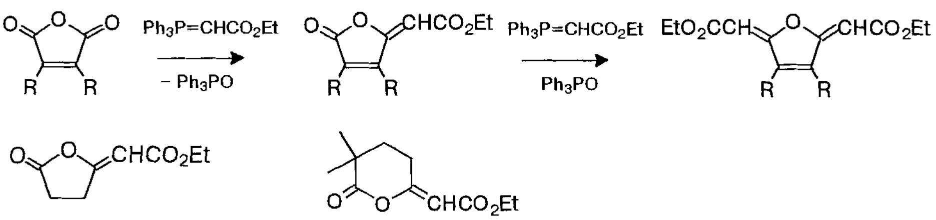
R=MeO, EtO, NAlk2, Me, Ph

(6.56)

Table 6.5. Reaction of $Ph_3P{=}CHC(O)R$ with phthalic anhydride (Eq. 6.56)[119]

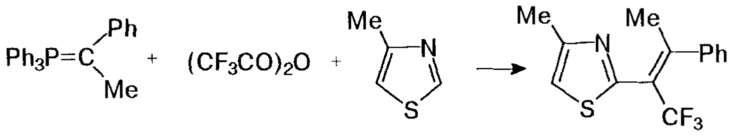
R	*Z*:*E* isomer ratio	
	100-120°C	40°C
EtO	1:10	2:9
Ph	4:1	1:10
Me	10:1	2:5

Wang and Li reported a convenient method for the synthesis of thunberginol F starting from the methoxyphthalide and 3,4-dimethoxybenzylide.[128] The reaction of succinic, maleic, phthalic, and glutaric acid anhydrides with ylides furnishes predominantly *E* isomers of lactones in yields of 70–98%.[124-128] Reaction with excess phosphorus ylides results in bis-olefins (Scheme 6.12)



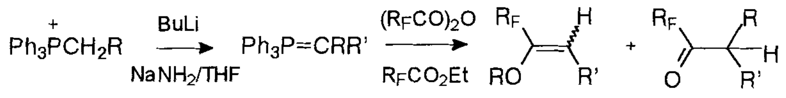
Scheme 6.12

A highly stereoselective route to fluorine-substituted vinylthiazoles and furans has been described (Eq. 6.57). The stereochemical purity of the products is occasionally 100%[128].



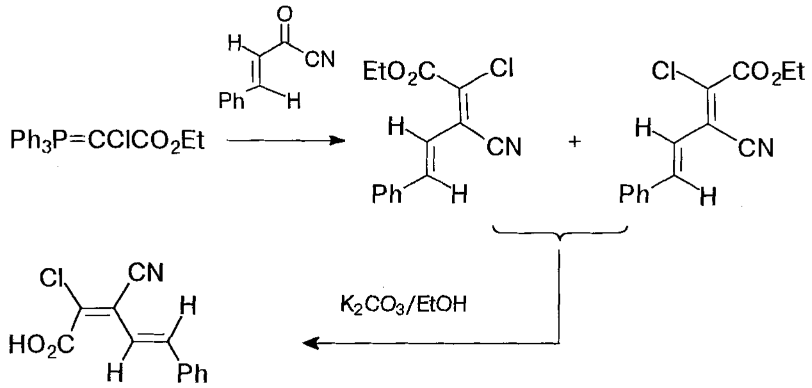
(6.57)

Shen and coworkers described the addition of trifluoroacetic anhydride to a P-ylide resulting in a 70% yield of ketone[129b]. However Begue and coworkers obtained only 30% yield when they tried to reproduce this experiment (Eq. 6.58)[91]: They reported that their attempts to acylate non-stabilized P-ylides with trifluoroacetic anhydride failed (either under salt-free conditions, or in the presence of lithium salts), probably because perfluoroalkyl anhydrides are unreactive with non-activated ylides[91].



(6.58)

2-Chloro-3-cyano-5-phenyl-2,4-pentandiene acids were prepared by the Wittig reaction of triphenylphosphonium ethoxycarbonylmethylide with cyanates in 70% yield (Scheme 6.13).[100]



Scheme 6.13

Miki et al reported the reaction of 1-benzylindole-2,3-dicarboxylic anhydride with Wittig reagents resulting in intermedites in the synthesis of murrayaquinone-A and ellipticine.[109]

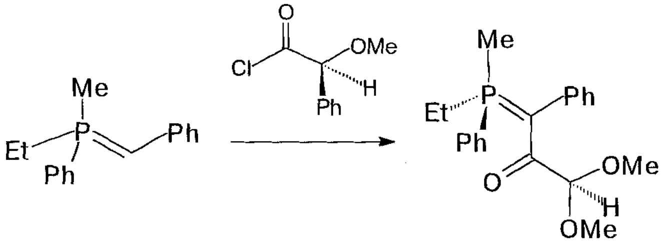
6.2.3 Asymmetric Wittig Reaction

Many attempts to develop an asymmetric version of the Wittig reaction have been reported over the past three decades[130–145], since the pioneering work of Bestmann and coworkers.[134] Several methods for the synthesis of chiral ylides were developed by MacEwen,[131] Bestmann,[133] Horner, and coworkers[130].

The possibility of performing an asymmetric version of the Wittig reaction. is not readily apparent as there are no new sp^3 stereocenters formed. However Wittig olefination reactions have been performed by placing stereogenic centers adjacent to or near the reaction center. Three types of asymmetric Wittig reaction have been achieved: kinetic resolution of racemic carbonyl compounds, desymmetrization of ketones, and preparation of optically active allenes.

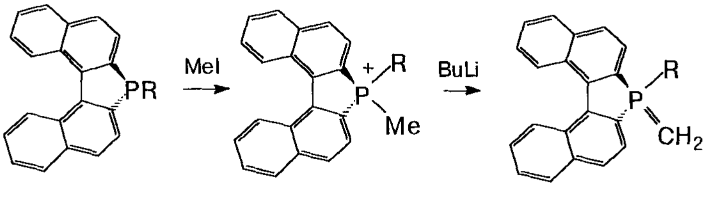
Chiral phosphonium salts have been converted to ylides by use of aqueous base or phenyllithium in ether, and the ylides were configurationally stable at phosphorus. This configurational stability of phosphorus persisted through alkylation, hydrolysis, reduction, and Wittig reactions as well as in reactions with epoxides[130–132].

Bestmann and Tomoskozi studied kinetic resolution in the 'umylidierung' reaction of racemic ylides with chiral acid chlorides, however the optical yield in this case was only 11–15.4% (Eq. 6.59)[133]:



(6.59)

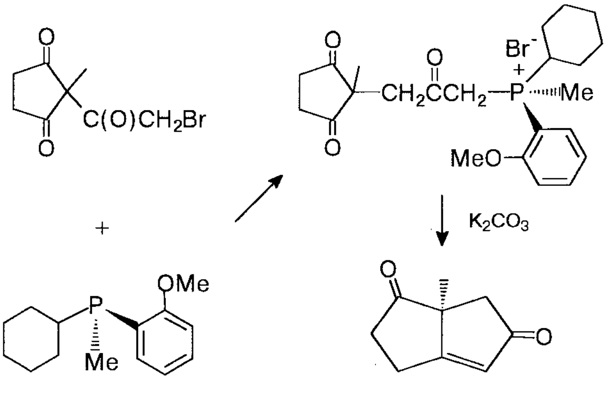
Fabbri and coworkers prepared chiral P-ylides from binaphthophospholes. The reaction of binaphthophospholes with methyl iodide gives phosphonium salts, which react with butyllithium to produce optically active phosphorus ylides (Eq. 6.60)[134]



(6.60)

Various variants of the asymmetric version of the Wittig reaction have been reported in the last few years[134–145]. Bestmann used chiral P-ylides for the synthesis of optical active allenes (Eq. 6.27) and cycloalkylidenes[133,137], and described asymmetric catalysis in the Wittig reaction[82].

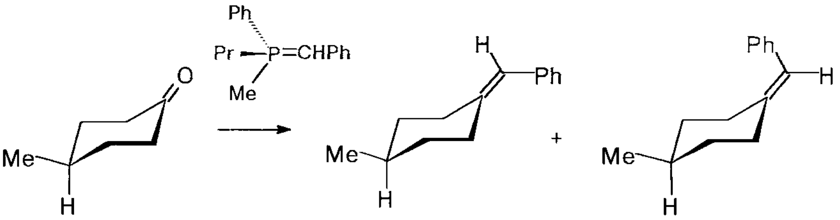
The easy reaction of ketene with P-ylides. provides the possibility of assembling compounds with axial chirality. Several attempts[138–143] have been documented. However early attempts had limited success and only low *ee* were reported. Fuji and coworkers[144] developed recently an asymmetric version in the preparation of an allene by a Wittig-type reaction and obtained optically active allenes in 71% yield and 81% *ee*. A strategy for disymmetrizing *meso*-triketone by intramolecular Wittig olefination has been adopted by Trost and Curran[145] in the synthesis of cyclopentanoid natural products. The bicyclic unsaturated diketone *S*-(+)-**14** was obtained in 77% *ee* by treatment of the chiral phosphonium salt with base (Scheme 6.14).



14

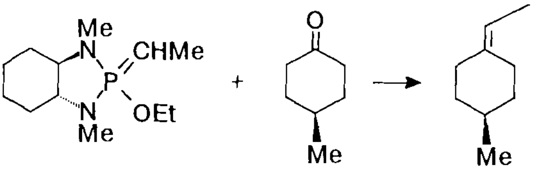
Scheme 6.14

The application of *ortho*- or *para*-substituted cyclohexanones leads to the formation of optically active topologically asymmetric cyclohexenes. The reaction of a chiral P-ylides with a 4-substituted cyclohexanone to give an axial dissymmetric olefin is the earliest attempted Wittig reaction. The first dissymetrization of 4-substituted cyclohexanones was reported by Bestmann and Lienert (Eq. 6.61)[82]:



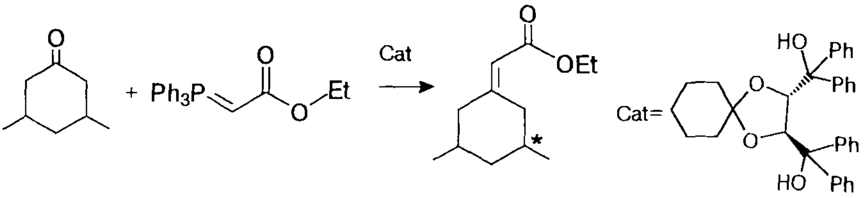
(6.61)

Bestmann and Lienert achieved reasonable asymmetric induction [43%] with chiral phosphonium ylide[82] and Hanessian developed a chiral phosphonamide ylide based on a C_2 cyclohexyl diamine for olefination that provides good control of stereochemistry at 'remote' centers[146]. Because the Wittig reaction does not create a new sp^3 carbon center, efforts to develop an asymmetric version of the Wittig reaction have been focused mainly on alkylidene-cycloalkanes with axial chirality. Their remarkable stereodifferentiating reactivity toward alkylcyclohexanones was demonstrated. Paramount in the design of these reagents was the inherent C_2 symmetry of the parent chiral diamines and the stereoelectronic consequences resulting from the spatial disposition of the heteroatom. By far the most selective direct transformations employ the chiral phosphonodiamides and menthyl phosphonoacetates with enantioselectivities of up to 90% for the elimination–coupling process with chiral sulfoximines (Eq. 6.62)



(6.62)

Desymmetrization was also realized by the reaction of an achiral ketone with an achiral P-ylide in the presence of a chiral inductor (Eq. 6.63).[147] This might provide opportunities for asymmetric catalytic ylide olefination[148].

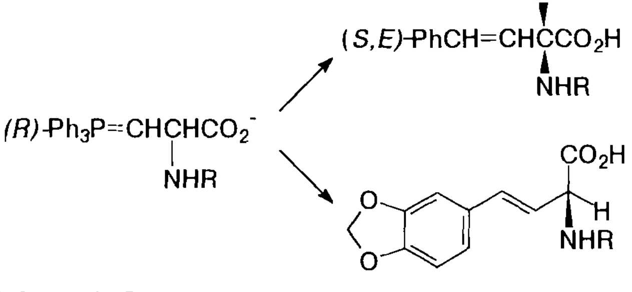


56.9% ee

(6.63)

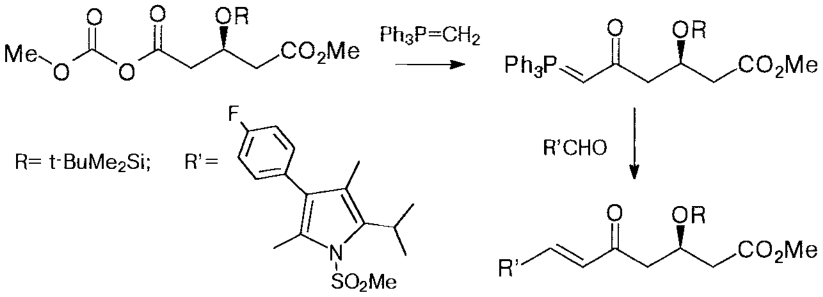
In the Wittig reaction with N-protected 3-(triphenylphosphono)alaninates, synthesis results in optically active *E*-(2-arylvinyl)glycine derivatives. Reaction with piperonal affords exclusively the *E* isomer with high optical purity (Scheme 6.15)[149]

McKervey and coworkers reported the use of the Wittig Reaction for the synthesis of homochiral N-protected α-aminoglyoxals[150] Chirality transfer from lactic acid derivatives was performed via [3,3]sigmatropic rearrangement to provide a simple route to both enantiomers of 1,2-aminoalcohols from a simple chiral precursor[151].



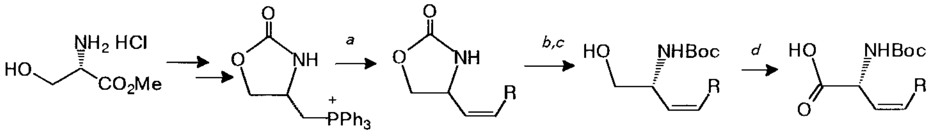
Scheme 6.15

Enantioselective preparation of optically pure *R* and *S* esters of 3-[(*tert*-butyldimethylsilyl)oxy] pentanedioic acid was developed by diastereoselective ring opening of 3-(*t*-butyldimethylsilyl)pentanedioic anhydride with benzyl *R*- and *S*-mandelate respectively (Scheme 6.16).



Scheme 6.16

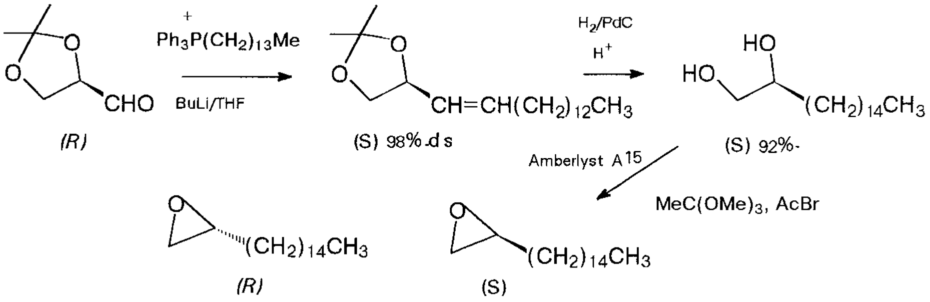
Wittig reaction with the phosphonium salt derived from serine proceeds with 93% retention of optical purity. Depending on the reaction conditions and the aldehyde high stereoselectivity was achieved in the synthesis of *a*,*β*-unsaturated amino-alcohols and amino acids (Scheme 6.17)[154]



a= RCHO; *b*=(Boc)2O/Et3N, *c*= LiOH; *d*=oxidation

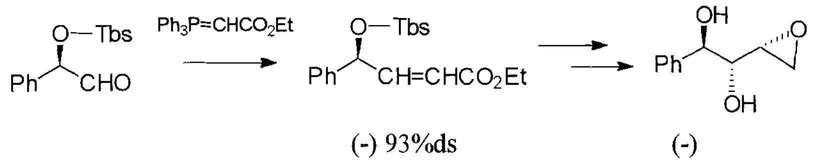
Scheme 6.17

Gandour and coworkers performed highly stereoselective synthesis of *R*- and *S*-pentadecyl-oxirane and transformed these into optically pure cyclic lipoidal ammonium salts which inhibit protein kinase C by binding at the regulatory site of the protein (Scheme 6.18)[155]:



Scheme 6.18

When heated under reflux in toluene the reaction of commercially available and cheap protected mandelic acid with P-ylide proceeds with 93% diastereoselectivity to afford the optically active ester; this was converted into an enantiopure epoxide, the precursor of (+)-goniodol (Eq. 6.64)[156]:



(6.64)

General articles are available which review asymmetric reactions of phosphorus ylides; these include a recent review of this author[148,157,158].

So, some excellent and synthetically promising work has been published on asymmetric reactions of phosphorus ylides. However the development of more efficient methods in this area are necessary—for example, the application of chiral catalysts and dynamic kinetic resolution of carbonyl compounds.

6.2.4 Experimental Conditions (Temperature, Pressure, Medium)

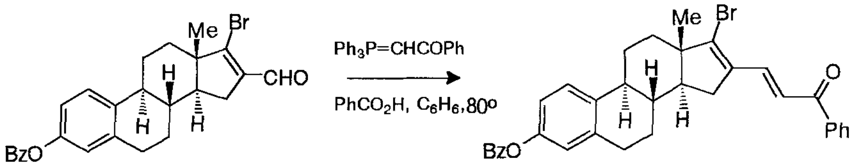
Reaction conditions (temperature, pressure, nature of solvent, dissolved additives, especially lithium halides, temperature, pressure, solvent) affect the rate and the stereoselectivity of the Wittig reaction.

6.2.4.1 Medium (Solvent and Additives)

Choice of solvent for the Wittig reaction depends on the character of the ylide. The Wittig reaction can be performed in solvents of various polarity—either non-polar (hexane, benzene), or highly polar (dimethylformamide, dimethyl sulfoxide). The nature of the solvent strongly affects the stereochemical result of the Wittig reaction and changes the Z:E isomer ratio of alkenes.

The presence of other substances strongly affects the rate, stereoselectivity, and, in some cases, regioselectivity of the Wittig reaction. Thus, lithium salts strongly influence the stereoselectivity of the Wittig reaction. They also catalyze the Wittig reaction of stabilized ylides with aldehydes and with ketones. In the presence of a larger quantity of lithium salts P-ylides undergo the reaction with ketones, with which they do not react under ordinary conditions[159–161].

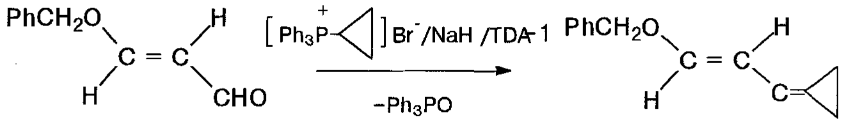
Benzoic acid catalyzes the Wittig reaction of stabilized ylides with aldehydes and ketones. Ruchard and coworkers reported that this acid catalyzes the Wittig reaction of triphenylphosphonium carboethoxymethylide with benzaldehyde, increasing yields of alkene[162], the rate of reaction[163], and E stereoselectivity. The inactivity of cyclohexanone toward $Ph_3P{=}CHCO_2Et$ can be overcome by addition of benzoic acid (0.3 equiv.) The effect of benzoic acid can be explained by protonation of the carbonyl oxygen making it more susceptible to attack by a weakly nucleophilic P-ylide. The application of benzoic acid in the reaction of triphenylphosphonium cyanomethylide with aldehydo sugars increased the amount of *trans* isomer formed[164,165]. The catalytic properties of benzoic acid have been used to stimulate the Wittig reaction in the synthesis of leukotrienes and prostaglandins[162,163,166,167]. Benzoic acid catalyzes the reaction of stabilized P-ylides with steroid ketones and increases the yield of the alkene to 95%. Tashiro and coworkers carried out the synthesis of 3-(estran-16-yl) acrylates with liquid crystalline properties by Wittig reaction in the presence of benzoic acid (Eq. 6.65)[168]:



(6.65)

Silica gel as an additive promotes the Wittig reactions of P-ylides with aldehydes, including sterically hindered aldehydes to increase the rate and yields of alkenes. However the *trans* selectivity of reaction decreases for aliphatic aldehydes[169].

The addition of small quantities of alcohols to organolithium alkylidene solutions increases the proportion of *E* isomers of alkenes[170]. Crown ethers influence the *Z*:*E* isomer ratio of alkenes in the Wittig reaction[171]. Stafford and McMurry[172] found, that yields of olefins prepared by Wittig reaction increase in the presence of phase-transfer catalyst TDA-1 :$N(CH_2CH_2OCH_2CH_2OMe)_3$.. Thus, β-benzyloxyacrylate reacts with a suspension of sodium hydride and cyclopropyltriphenylphosphonium bromide in THF in the presence of TDA-1 with the formation of benzyl oxypropenylidene cyclopropane in 83% yield, whereas in the absence of TDA-1 the reaction does not proceed (Eq. 6.66). The influence of additives on the Wittig reaction is summarized in Table 6.6.



(6.66)

Table 6.6. Influence of additives on the Wittig reaction

Additive	Influence of additives on:			Ref.
	Yield (%)	Rate	Stereoselectivity	
Lithium salts	+	+	*E*	159–161
$PhNEt_2$	−	−	+	307
Crown ethers	−	−	+	171
Benzoic acid	+	+	−	162,163,166,167
Silica gel	+	+	−	169
$N(CH_2CH_2OCH_2CH_2OMe)_3$	+	+	*Z*, *E*	172
Cyclodextrins	+	−	+	173
Glass beads	−	+	−	174

The Wittig reaction in the presence of the sodium amide as a base and glass beads, facilitating the mixing of reagents, results in very high yields of *Z*-1,11-dienes[174]. Cyclodextrins increase *Z*:*E* selectivity of the Wittig reaction of semi-stabilized ylides with aromatic aldehydes[173]. *Z* selectivity of the reaction was greater than 92% and *E* selectivity was 80%. Sterically hindered substituents preventing complexation with cyclodextrins reduce the selectivity[173].

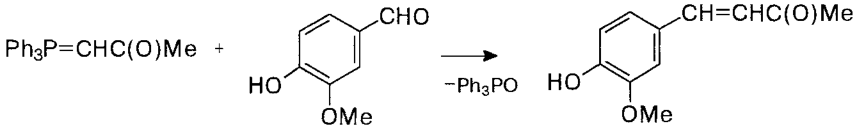
6.2.4.2 Temperature

Variations in temperature affect the rate of the Wittig reaction but do not have a significant effect on the *Z*:*E* stereoselectivity. The choice of the temperature of the Wittig reaction depends on the activity of the starting reagents. The Wittig reaction of non-stabilized ylides with carbonyl compounds must be cooled to –78°C. Semi-stabilized ylides react at room temperature or with gentle cooling. For instance, triphenylphosphonium benzylide reacts with benzaldehyde in 5 min at 10°C to give stilbene in 78% yield[175] and stabilized ylides, because of reduced nucleophilicity, enter to the Wittig reaction on heating. Triphenylphosphonium carboethoxymethylide reacts with cyclohexanone only at 100°C to afford the ethyl cyclohexylideneacetate in 60% yield[176]. Tributylphosphonium fluorenylide reacts with 4,4′-dinitrobenzophenone when heated under reflux in chloroform for 3 h to afford the olefin in 15% yield; when heated for 24 h the yield is 93%[8]. High temperature must be used to effect the Wittig reaction with hindered or unreactive ketones.

6.2.4.3 Pressure

The Wittig reaction of phosphorus ylides is facilitated by use of pressure, which enhances the rate of reaction and yields of alkenes[177–181].

Isaacs and coworkers performed kinetic measurements and calculated activation volumes ΔV^{P} of the reaction of phosphorus ylides with carbonyl compounds. Depending on the nature of the solvent the negative values of ΔV^{P} for the reaction change from –20 to –30 $cm^3 \cdot mol^{-1}$ in. The authors came to the conclusion that the pressure increases the rate of reaction, and the optimum pressure for acceleration of the Wittig reaction is 10 kbar[178]. Nonnenmacher and coworkers[179] confirmed that the rate of the Wittig reaction of stabilized ylides increases with increased pressure (Eq. 6.68):



(6.68)

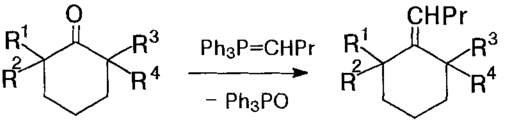
The yields of alkene in the reaction of triphenylphosphonium acetylmethylide with 3-methoxy-4-oxybenzaldehyde at 27°C for 6 h varied depending on the pressure according to the sequence:

p (kbar)	1.3	3	5	9	10
Yield (%)	17	23	24	61	65

The *Z:E* isomer ratio depends little on the variation of pressure. Isaacs and coworkers[178] studied the reaction of triphenylphosphonium carboalkoxyalkylides with a number of ketones at 9–10 kbar and found that yields of tri- and tetrasubstituted ethylenes were considerably higher than at atmospheric pressure Reaction of triphenylphosphonium carboethoxymethylide with diethylketone is very slow at atmospheric pressure even in refluxing xylene; at 9 kbar and 50°C the olefin is formed in 70% yield (Eq. 6.69)[180]:

$$Ph_3P{=}C(R')CO_2Et + Et_2C{=}O \longrightarrow Et_2C{=}C(R')CO_2Et \qquad (6.69)$$

Dauben and Takasugi[181] investigated the Wittig reaction of the triphenylphosphonium butylide with sterically hindered cyclohexanones (Eq. 6.70). Except for 2,2;6,6-tetramethylcyclohexanone and fenchone, increasing the pressure from 7 to 15 kbar at a constant temperature of 40°C increased yields from 45 to 60%, depending on the steric influence of substituents on the carbonyl group; at ordinary pressure the reaction did not proceed.

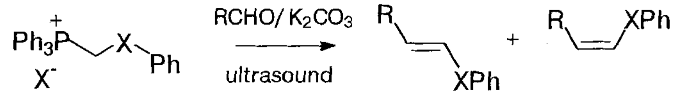


(6.70)

To some extent the use of high pressure has a similar effect to increasing the temperature. This can be useful for thermally unstable compounds, when the Wittig reaction cannot be performed by heating.

6.2.4.4 Sonication

Ultrasound catalyzes the Wittig reaction. Application of ultrasound irradiation substantially improves the course of the reactions and accelerates the formation of alkenes[182]. Sonication catalyzes the Wittig reaction to give olefins faster and in higher yields than the use of interphasic conditions (Eq. 6.71)[183,187]:

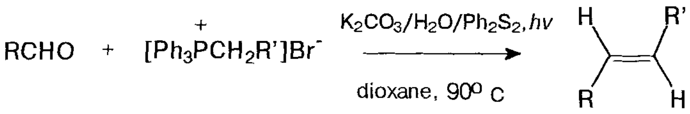


(6.71)

X=S, Se; R= i-Pr, Ar; Z:E = 25:75-64:36

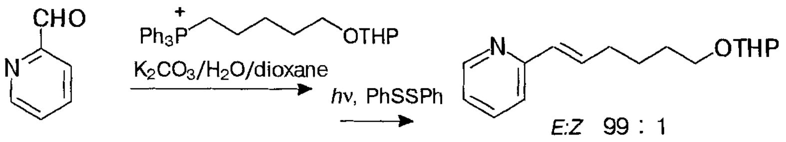
6.2.4.5 Irradiation

Irradiation with daylight affects the stereoselectivity of the Wittig reaction. Thus Matikainen and coworkers reported that irradiation with a daylight lamp of the reaction of aldehyde with ethyltriphenylphosphonium bromide in the presence of potassium carbonate as a base furnishs olefins in high yields and with 98% *E* isomeric purity (Eq. 6.72)[184-187]:



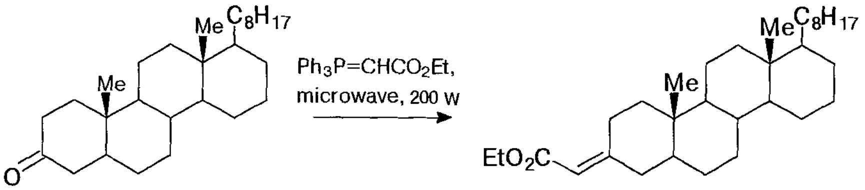
(6.72)

The key step in the syntheses of isopulo'upone, a marine product, includes the Wittig reaction between 2-picolinaldehyde and ylide generated from 5-(2-tetrahydropyranyoxy)pentylphosphonium salt (Eq. 6.73). The reaction mixture was irradiated with a daylight lamp in the presence of diphenyl disulfide to give isopuloupon in >98% stereochemical purity[184].



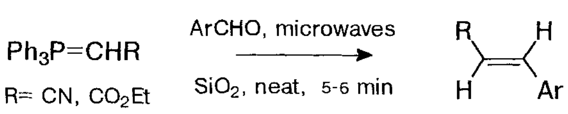
(6.73)

Microwave irradiation accelerates some difficult Wittig reactions of salts-free stable ylides with various ketones. Irradiation in a domestic microwave oven of the mixture of reactants, in the absence of solvent, resulted in improved yields of olefins more rapidly than with conventional heating (Eq. 6.74; Eq. 6.75). Microwave irradiation with high pressure and ultrasound are the most promising unconventional methods used nowadays in organic synthesis[185,187].



(6.75)

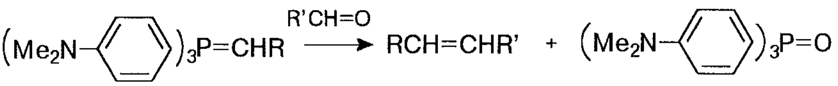
The Wittig reaction of stable ylides with aromatic aldehydes with microwave heating results in remarkable rate enhancement, dramatic reduction of reaction times, and improved yields of reaction products (Eq. 6.76)[186a,b,187a,b]:



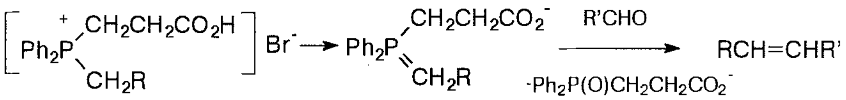
(6.75)

6.3 Advanced Methods

The experimental conditions of the Wittig reaction are comparatively simple. In general 2–3 equiv. triphenylphosphonium salt and 4–6 equiv. base in THF can be used for best product yields. The best method for performing the Wittig reaction consists in *in situ* generation of ylide from phosphonium salt in the presence of carbonyl compound via dropwise addition of a base to a reaction mixture. The treatment of prepared phosphorus ylide by carbonyl compound provides, after completion of the reaction, olefin and triphenylphosphine oxide. The reaction can be monitored by IR or NMR spectroscopy or chromatography; usually thin-layer chromatography (TLC) is used to monitor the disappearance of the spot corresponding to the carbonyl compound. Analysis of the *E*/*Z* ratio of alkene isomers can be accomplished either by ^{1}H NMR. The ratio is obtained by integration of the olefinic proton of the product acids or their esters. Gaseous and high-performance liquid chromatography are also used. Preparative column chromatography is usually used for isolation and purification of reaction products. Triphenylphosphine oxide is usually separated by addition of hexane to the reaction mixture or by column chromatography. Improved methods have been proposed for separating the phosphine oxide and alkenes formed during the reaction.[188-195] For instance, Fukumoto and Yamamoto suggested separating phosphine oxide from alkene by dissolution and separation of phases[190], and also by addition of deionized water to the THF solution[191]. After treatment with hydrochloric acid, triarylphosphine oxides containing a dialkylamino group in the benzene ring do not dissolve in hydrocarbons and can be separated (Eq.6,76)[188]. Those phosphorus ylides which are derivatives of β-diphenyl-phosphinopropionic acid furnish, after Wittig reaction, phosphine oxides which are readily soluble in water and insoluble in hydrocarbons; this facilitates their separation from the olefins (Eq. 6.77)[189].

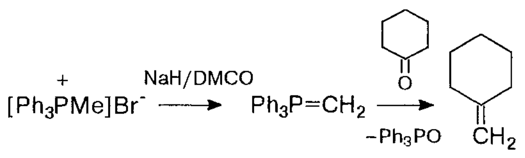


(6.76)



$$\left[Ph_2\overset{+}{P}\begin{matrix}CH_2CH_2CO_2H\\CH_2R\end{matrix}\right]Br^- \longrightarrow Ph_2P\begin{matrix}CH_2CH_2CO_2^-\\CH_2R\end{matrix} \xrightarrow[-Ph_2P(O)CH_2CH_2CO_2^-]{R'CHO} RCH{=}CHR' \quad (6.77)$$

The reaction can be also performed in high-boiling solvents (DMSO, mesitylene) to facilate the separation of olefins from phosphine oxides as the next examples show (Eq. 6.78; Eq. 6.79).

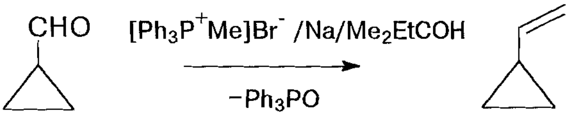


(6.78)

Methylenecyclohexane (Eq. 6.78)[192]

Sodium hydride (0.1 mol of 55% suspension in mineral oil) was washed several times with pentane to remove the mineral oil. Then flask containing the sodium hydride was filled with inert gas and DMSO (50 mL) was introduced. The reaction mixture was heated under reflux with stirring up to termination of the elimination of hydrogen (~45 min). The prepared solution of dimsyl sodium in DMSO was cooled in an ice bath and methyltriphenylphosphonium bromide (35.7 g, 0.1 mol) in warm DMSO (100 mL) was added to a give red solution of the ylide. After 10 min freshly distilled cyclohexanone (10.8 g, 0,11 mol) was added to the ylide and the reaction mixture was stirred at room temperature for 30 min. The methylenecyclohexane was then distilled under vacuum into a trap cooled to −70°C. Yield 8.1 g (86.3%), bp 42°C (10 mmHg).

Sodium *tert*-amylate was used to generate of phosphorus ylide make use of (*Conia–Dauben modification of the Wittig reaction*). The reaction has been performed in mesitylene, to facilitate the distillation of the reaction product. By this method Tsunoda and Hudlicky[193] obtained vinylcyclopropane of the high purity (Eq. 6.79):



(6.79)

Vinylcyclopropane (Eq. 6.79)[193]

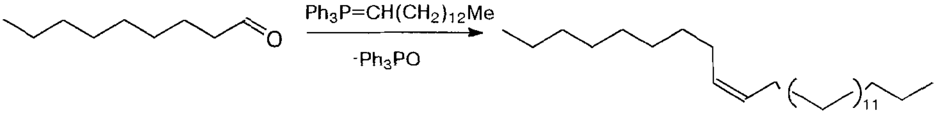
Methyltriphenylphosphonium bromide (25.5 g, 0.0714 mmol) was suspended in absolute mesitylene (80 mL) and a solution of freshly prepared sodium *tert*-amylate (42.8 mL, c 2.0 M) was added. The reaction mixture was stirred for 30 min at room temperature and then cyclopropylaldehyde (2.5 g, 0.0357 mol) in mesitylene (10 mL) was added. The reaction mixture was heated under reflux for 2 h under argon, then cooled and transferred to a Claisen flask equipped with 40 cm column. Vinylcyclopropane was distilled into a flask cooled with dry ice Yield 1.51 g (62.9%), bp 38–39.5°C. The purity of the product is 99%.

During recent years several improvements of the Wittig reaction have been developed.

6.3.1 Instant Ylide Mixtures

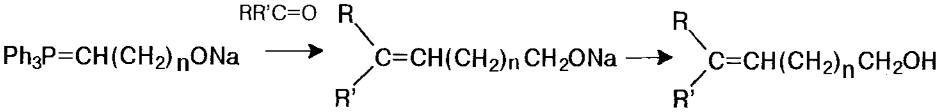
An iproved laboratory methodology of the Wittig reaction was proposed by Schlosser[194-196]. Instant ylide mixtures consist of dry sodium amide powder[194] or potassium hydride[196] and phosphonium salt, which are well preserved in a closed flask and are easily dispensed.

Although the reaction does not proceed in the absence of solvent, addition of ester to the mixture activates the formation of salt-free phosphorus ylides which react with aldehydes to form olefins with a high *Z* isomer content. For instance, by this method Moiseenkov and Schlosser[195] obtained the pheromone of the domestic fly 'Muscalur' in 81% yield and with a *Z*:*E* isomer ratio of 97.5:2.5 (Eq. 6.80):



(6.80)

Phosphonium salts bearing hydroxy- and amino groups mixed with sodium amide can be stabilized by covering the particles of the sodium amide with paraffin. Addition of THF to solid mixtures of ω-hydroxyalkyltriphenyl-phosphonium salts and paraffin-coated amide afford the phosphorus ylide solution after several minutes. Reaction of 1 equiv. phosphonium salt with 2 equiv. sodium amide produces the triphenylphosphonium ω-sodiumoxidoalkylide in quantitative yield; this then undergoes the Wittig reaction with aldehydes and with ketones to afford alkenolates which, after hydrolysis, furnish alkenols (Eq. 6.81)[196]:



$$Ph_3P{=}CH(CH_2)_nONa \xrightarrow{RR'C{=}O} \overset{R}{\underset{R'}{\diagdown\!\!\diagup}}C{=}CH(CH_2)_nCH_2ONa \longrightarrow \overset{R}{\underset{R'}{\diagdown\!\!\diagup}}C{=}CH(CH_2)_nCH_2OH$$

(6.81)

The reaction furnishes alkenols with high stereoselectivity (Z:E isomer ratio 98:2).

Z-Tetradecen-1-ol (Eq. 6.82)[195]

(a) Dry powdered sodium amide (2.1 mol, 80 g) was mixed with melted paraffin (160 g) at 65°C in a round-bottomed flask under an inert atmosphere. After 10 min mixing with a magnetic stirrer the suspension was cooled on a bath of dry ice and carefully grated. The paraffin-coated sodium amide was the mixed with 6-hydroxyhexyltriphenyl-phosphonium bromide (1.0 mol, 460 g; the rotor distillator can be used). The instant ylide reagent is ready for application

(b) THF (100 mL) was added to this reagent (25 mmol, 17.5 g) in three-necked flask and stirred for 30 min at 25°C. The solution was then cooled to –80°C and octanal (25 mmol) was added. After 15 min the mixture was heated to 25°C, diluted with pentane (100 mL) and the precipitate was separated. The suspension was washed once more with a mixture of pentane with dichloromethane (100 mL) then ether (50 mL) and water (10 mL) was added. The ether layer was dried with potassium sulfate, the solvent was evaporated, and the residue was distilled. Yield 3.9 g (73%), bp 87–90°C (0.1 mmHg).

6.3.2 Inter-Phase Transfer Conditions

The most recent perfection of the Wittig reaction is phase-transfer catalysis[197-220]. The application of this method enables avoidance of the use of such strong bases as butyllithium, sodium hydride, and sodium amide. Replacement by aqueous solutions of alkalis enables simplification of the technology of reaction. There are two modifications of the Wittig reaction under phase-transfer conditions: liquid–liquid[197-220] and solid–liquid[221-245].

6.3.2.1 Liquid–Liquid

The preparation of ylides from phosphonium salts under liquid–liquid phase-transfer conditions with aqueous and organic layers can be performed in the absence of complementary catalysts, because the phosphonium salts are simultaneously reagents and the agents of inter-phase transfer. The Wittig reaction can as well be performed in the presence of phase-transfer catalysts (e.g. quaternary ammonium salts).

During dehydrohalogenation of phosphonium salts the proton is transferred across the phase boundary; the ylides thus dissolve in the organic solvent and undergo the Wittig reaction. The preparation of non-stabilized ylides under phase-transfer conditions can, in principle, be accompanied by hydrolysis with the formation of phosphine oxides. However usually the Wittig reaction of phosphorus ylides with carbonyl compound proceeds faster, than hydrolysis.

Markl[205] showed that the dehydrochlorination of phosphonium salts in 50% aqueous sodium hydroxide with dichloromethane as organic solvent gives phosphorus ylides undergoing reaction with benzaldehyde with the formation of olefins in 30–50% yields (Eq. 6.83):

$$[Ph_3\overset{+}{P}CHR^1R^2]Cl^- \xrightarrow{NaOH/H_2O/CH_2Cl_2} Ph_3P{=}CR^1R^2 \xrightarrow[-Ph_3PO]{R^3CHO} R^3CH{=}CR^1R^2 \qquad (6.83)$$

The yields of olefins increase substantially (to 60–88%) when the α carbon atom contains any acceptor of electrons, for instance a phenyl group.

Syntheses of cis- and trans isomers of stilbene[205]

Sodium hydroxide (50%, 10 mL) was added to a mixture of benzaldehyde (2.06 g), benzyltriphenylphosphonium chloride (7.86 g), and dichloromethane (10 mL) with vigorous stirring. After 30 min the organic layer was separated, washed with water, and dried with calcium chloride. The solvent was separated, alcohol (15 mL) was added and the mixture was cooled with ice. Crystalline *trans*-stilbene (1.2 g, 33%) was separated, mp 123–124°C. *cis*-Stilbene (1.7 g, 47%; bp 60–62°C, 0.01 mmHg) was isolated from the filtrate.

Two-phase-transfer catalysis is widely applied for the generation of triphenylphosphonium ylides. Reaction of alkyltriphenylphosphonium salts with aromatic aldehydes in aqueous alkali–benzene solution ensures high (or, from aliphatic aldehydes, satisfactory) yields of olefins (Eq. 6.84, Table 6.7) [208].

$$[Ph_3\overset{+}{P}CH_2R^1]Cl^- + R^2CHO \xrightarrow[-Ph_3PO]{NaOH/H_2O/C_6H_6} R^2CH{=}CHR^1 \qquad (6.84)$$

The ratio of starting reagents and temperature affect the Wittig reaction in aqueous alkali–benzene solutions. The highest yield of olefins, 95–99%, were obtained when the reaction was performed at room temperature for one or several days.[208].

Table 6.7. Conditions and yields of the Wittig reaction under phase-transfer conditions (Eq. 6.84)

R^1	R^2	X	t (h)	C_{NaOH} (mol L^{-1})	T (°C)	Yield (%)	Ref.
H	Ph	I	24	5	40	99	208
H	$4\text{-}ClC_6H_4$	I	24	5	24	95	208
H	$4\text{-}MeC_6H_4$	I	44	5	24	95	208
H	$4\text{-}MeOC_6H_4$	I	44	5	24	38	208
H	C_7H_{15}	I	48	5	24	73	208
H	α–Furyl	I	90	5	24	63	208
H	PhCH=CH	I	90	5	24	68	208
Ph	Ph	Cl	24	5	24	81	208
Ph	C_7H_{15}	Cl	5	5	24	82	208
Ph	PhCH=CH	Cl	44	5	24	71	208
$CH_2{=}CH$	Ph	Cl	0.5	0.5	24	60	208
$CH_2{=}CH$	C_7H_{15}	Cl	0.5	0.5	24	60	208
Me	Ph	Br	24	0.5	24	46	78
C_5H_{11}	Ph	Br	24	1.5	24	46	208
Naphthyl monosaccharide							211

General method for the Wittig reaction under phase-transfer conditions (Eq. 6.84)[208]

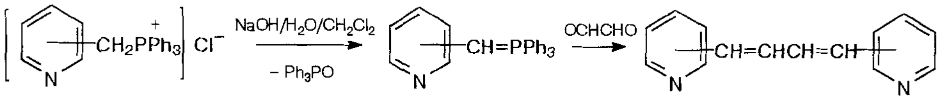
A mixture of alkyltriphenylphosphonium halide (3 mmol), aldehyde (1.5 mmol), petrol (3 mL), and an aqueous solution of alkali (9 mL) was stirred for several days (24–90 h) at room temperature. The reaction was monitored by thin-layer chromatography. The benzene extract contained the olefin and phosphine oxide, and these were separated by conyentional methods (Table 6.7). The concentration of alkali depends on the structure of the phosphonium salt: for methyltriphenylphosphonium halide 5 n NaOH was used; for benzyl and propyltriphenylphosphonium bromide 15 n NaOH.

Z:*E* isomer ratio of the Wittig reaction under phase-transfer conditions depends on the solvent, especially for non-stabilized ylides[171]. Poly(ethylene glycol) increases the yields of olefins (Eq. 6.85)[206]:

$$\overset{+}{[Ph_3PCH_2R]}\,X^- + R'CHO \xrightarrow{K_2CO_3/H_2O/Solvent} R'CH{=}CHR \qquad (6.85)$$

$R{=}Ph, Me, CO_2Me, R'{=}Ph, 4\text{-}MeOC_6H_4; X{=}Et$

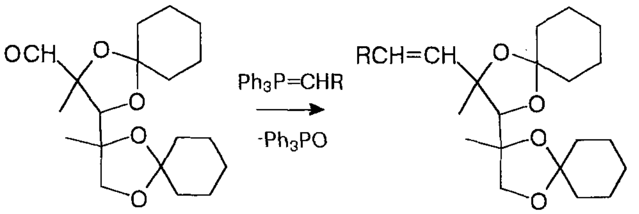
The Wittig reaction between pyridylmethyl- and quinolylmethylphosphonium salts and 40% aqueous glyoxal in 50% aqueous sodium carbonate and dichloromethane enabled the preparation of 1,4-dipyridyl- and 1,4-diquinolyl-1,3-butadiene in good yields (Eq. 6.86)[210]:



(6.86)

The Wittig olefination of aldo isomers of sugars with phosphonium salts under phase-transfer conditions in the presence of TEBAC furnishes 75–85% yields in the system benzene–50% NaOH and 45–65% yields in the system benzene–DMSO–K_2CO_3 (Eq. 6.87)[211].

The two-phase Wittig olefination of water-soluble aldehydes (formaldehyde, glyoxal) has been described[210,212]. Syntheses of 2-vinylbenzimidazole from formaldehyde and appropriate phosphonium salts was performed in the system water–chloroform–Na_2CO_3[210]. The reaction of methyltriphenyl- and benzyltriphenyl-phosphonium salts with ferrocene-aldehyde in the system benzene–25% NaOH–TEBAC furnishes 80–85% yields of vinylferrocene and phenylvinylferrocene as a mixture of *Z* and *E* isomers[213].



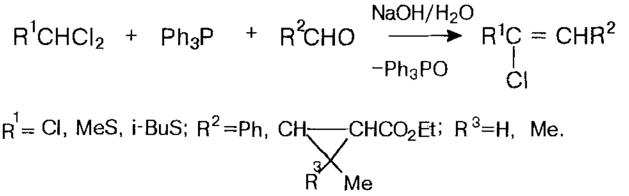
(6.87)

R = naphthyl-1, 4-$O_2NC_6H_4CH$=CH, 1-methylbenzoylidasolyl-2, benzoylidazolyl-2,1.5-dimethylbenzoyliodazolyl-2,1-methyl-5-nitrobenzoilidazolyl-2.

A simple method has been proposed for the Wittig reaction of phosphonium salts with aromatic aldehydes which enables the preparation of olefins containing 70–84% of the *Z* isomer[214]. Treatment of a polygalohenemethane mixture of triphenylphosphine and aldehydes with concentrated aqueous alkali under phase-transfer conditions affords the corresponding olefins, including derivatives of chrysanthemic acid (Eq 88). This reaction probably proceeds via the formation of carbenes[215].

2-Methylthio-2-chlorostyrene (Eq. 6.88)[215]

An aqueous solution of sodium hydroxide (40%, 15 mL) was added dropwise with vigorous stirring to a solution of α,α-dichlorodimethyl sulfide (6.6 g, 0.05 mol), benzaldehyde (6.3 g, 0.05 mmol), and triethylbenzylammonium chloride (0.23g, 1 mmol) in benzene (25 mL). The temperature of the reaction mixture increased from 20 to 30°C. The mixture was left for 30 min at this temperature and then benzene (40 mL) and water (40 mL) were added The organic layer was separated, washed with water (30 mL), dried with sodium sulfate, and evaporated under reduced pressure. Treatment of the residue with ether (50 mL) furnishes triphenylphosphine oxide (11 g) which was removed by filtration. The ether solution was evaporated, the residue was distilled in vacuo, and the central fraction boiling at 112–115°C (1.5 mmHg) was collected. Yield 3.8 g (44%).

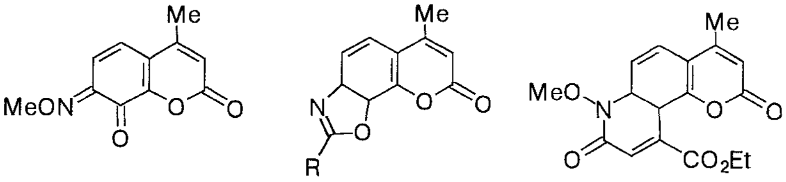


$$R^1CHCl_2 + Ph_3P + R^2CHO \xrightarrow[-Ph_3PO]{NaOH/H_2O} R^1\underset{\displaystyle Cl}{C}=CHR^2 \qquad (6.88)$$

The influence of solvent, concentrations, and temperatures on the reaction was studied[216]. Kinetic studies of the Wittig reaction of benzaldehyde with benzyltriphenylphosphonium bromide in the biphasic system sodium hydroxide–water–dichloromethane showed that the mechanism of replacement was S_N2 (Eq. 6.89)[217,218]:

$$[Ph_3\overset{+}{P}CH_2Ph]Br^- + PhCHO \xrightarrow[-Ph_3PO]{NaOH/H_2O/CH_2Cl_2} PhCH=CHPh \qquad (6.89)$$

The preparation of some 9-vinylacrydines by the Wittig reaction under phase-transfer catalysis was described by Vlassa and coworkers.[219] Keto- and ester-stabilized ylides react with 7-(methoxyimino)-4-methyl-2*H*-chromene-2,8(7*H*)-diene under phase-transfer conditions to give benzopyranooxazol-8-ones or pyridones (Eq. 6.90)[108]:



(6.90)

Listvan described the synthesis of cholesteric esters of unsaturated acids as liquid crystals by Wittig reaction.[220a]

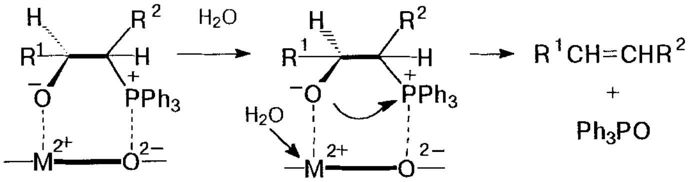
6.3.2.2 Solid–Liquid

It is known that reactions in heterogenous media are often more selective than in homogenous solutions, and that isolation of products is easier.[220-243] The Wittig reaction has been performed with solid catalysts such as alumina, potassium hydroxide, potassium carbonate, alumina-supported potassium fluoride, or barium hydroxide.[221-224]

The Wittig reaction of triphenylphosphonium phenacylide with substituted benzaldehydes in aqueous dioxane (30:0.5) in the presence of solid barium hydroxide at 70 °C affords olefins in very high yields (Eq. 6.91)[223]:

$$[Ph_3\overset{+}{P}CH_2C(O)Ph]Br^- + ArCHO \xrightarrow[-\,Ph_3PO]{Ba(OH)_2/C_4H_8O_2/H_2O} ArCH=CHC(O)Ph \qquad (6.91)$$

Foucaud and coworkers[221] found, that solid zinc and magnesium oxides are effective catalysts of the Wittig reaction. The addition of small amounts of water to the magnesium oxide (4 g water for 5 g of MgO) increases the reaction rate whereas addition of water to zinc oxide does not affect the reaction (Table 6.8)[225], because Zn^{2+} forms more stable complexes with oxygen of the betaine, than Mg^{2+} (Scheme 6.19) and so the water cannot cleave the coordination bond of the betaine if Zn^{2+} is present on the surface.



Scheme 6.19

Table 6.8 Conditions for performing the Wittig reaction in heterogeneous media (Eq. 6.92)

$$[Ph_3PCH_2R_2]\ Cl^- + R^1CHO \longrightarrow R^1CH{=}CHR^2 + Ph_3PO \qquad (6.92)$$

R^1	R^2	Base	*t* (h)	*T* (°C)	Yield (%)	Ref.
Ph	CN	MgO	2	20	87	221
i-Pr	CN	MgO	24	20	32	221
$4\text{-}ClC_6H_4$	CN	MgO	4	60	65	221
Ph	CO_2Et	MgO	4	20	79	221
$4\text{-}ClC_6H_4$	CO_2Et	MgO	4	60	60	221
Ph	Ph	MgO	24	20	30	221
Ph	CN	ZnO	24	20	80	221
Ph	Ph	ZnO	24	20	25	221
Ph	$CH{=}CH_2$	K_2CO_3	2	76	95	226
$PhC{\equiv}C$	C_6H_{13}	K_2CO_3	3	125	76	225

Methods for the Wittig reaction in the presence of solid catalysts (Table 6.8, Eq.92)
Method A[221] Solid catalyst (zinc or magnesium oxide, 4 g) was added in small portions to a stirred equimolar mixture of aldehyde and phosphonium salt (10 mmol). The heterogeneous mixture was left at room temperature for a time shown in Table 6.9. After addition of diethyl ether, the inorganic solid was removed by filtration. The triphenylphosphine oxide was precipitated by addition of pentane. Evaporation of the solvent under reduced pressure afforded the olefin, which was purified by distillation or crystallization.
Method B[93] A mixture of alkyltriphenylphosphonium bromide (15 mmol), K_2CO_3 (3 g), solvent (15 mL), water (0.1 mL), and aldehyde (15 mmol) was heated (bath temp. ≈125°C) for 3 h. The reaction mixture was then cooled, the precipitate was removed by filtration, and the solvent was evaporated. The residue was extracted with pentane (6 × 50 mL) and the extract was stored under refrigeration overnight. The triphenylphosphine oxide was removed by filtration, the solvent was evaporated, and the residue was chromatographed with SiO_2 (pentane as eluent)

Husid and Kovalev[225] showed that heating of alkyltriphenylphosphonium salts with solid potassium carbonate in organic solvents generated ylides which underwent the Wittig reaction with saturated *a,β*-ethylenes, *a,β*-acetylenes, and cycloaliphatic aldehydes to produce in olefins in very good *Z* stereoselectivity (*Z*:*E* = 20:80–0.3:99.7) (Eq. 6.93):

$$[Ph_3\overset{+}{P}CH_2R']Br^- + RCHO \xrightarrow{K_2CO_3} RCH{=}CHR' \qquad (6.93)$$

R=C_6H_{13}, $C_6H_{13}CH{=}CH$, $C_6H_{13}C{\equiv}C$, PhC≡C, c-Pr, geranyl; R'=Et, C_6H_{13}

The best results were obtained with solid potassium carbonate in benzene, toluene, dioxane, or tetrachloroethylene[225–229]. Conjugated dienes were obtained in high yields by reaction of aldehydes with phosphonium salts under two-phase conditions, i.e. solid–liquid medium. Reaction was performed in boiling toluene in the presence of solid potassium carbonate[244]. Upon heating of the phosphonium salt with K_2CO_3 at 125°C in tetrachloroethylene 4-undecene was obtained in 90% yield The isomeric composition of olefins synthesized from phosphonium salts in aprotic solvents under phase-transfer conditions is identical with the composition of olefins prepared with salt-free ylides. Alternatively, the use of alkaline carbonates in slightly hydrated solid–liquid protic organic media enables the Wittig reaction of polyfunctional aldehydes with non-stabilized and semistabilized ylides resulting in alkenes in high yields and *E* preferential stereochemistry (Eq. 6.94)[230–233]:

$$PhCHO + [Ph_3\overset{+}{P}CH_2R]Br^- \xrightarrow[-Ph_3PO]{K_2CO_3/MeOH} PhCH{=}CHR \qquad (6.94)$$

R=Pr, 4-C_6H_4Me, 4-C_6H_4OMe, furyl

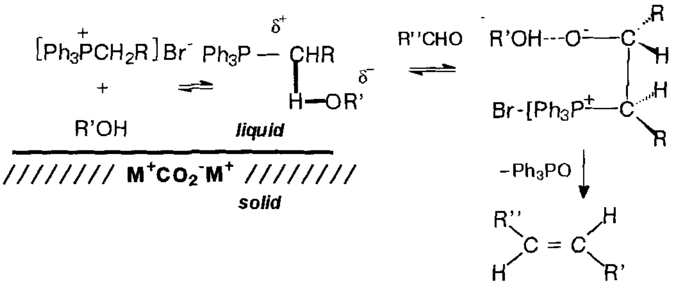
Reaction is complete in 1 h at 65°C and results in the olefin (R = Pr) in 72% yield containing 75% of the *E* isomer. Increasing the reaction temperature to 80°C in isopropanol increased the yields of olefins to 98% and the content of *E* isomer to 79%. The effects of the nature and concentration of protic additives on the yields and stereoselectivity of the Wittig reaction are shown in Table 6.9

$$PhCHO + [Ph_3P^+(CH_2)_3CH_3]Br^- \xrightarrow{K_2CO_3/dioxane/ROH} PhCH{=}CH(CH_2)_2CH_3 \qquad (6.95)$$

Table 6.9 The Wittig reaction in the presence of K_2CO_3 (Eq. 6.95)[230]

C_{ROH}		Yield (%)	*E*:*Z*
R = H	R = Me		
1.67	–	98	21/79
	1.67×10^{-2}	19	21/79
	3.34×10^{-2}	37	22/78
	5.01×10^{-2}	59	25/75

Le Bigot[230] proposed a mechanism explaining the high *E* selectivity of the reaction (Scheme 6.20). Accordingly to Le Bigot's mechanism the high yields of olefins with preferential *E* isomer content was a result of solvation of ionic intermediates by alcohol.



Scheme 6.20

The methodology developed by Le Bigot results in the maximum yields of olefins (62–92%) in the Wittig reaction of aldehydes with non-stabilized ylides in two-phase media in the presence of potassium carbonate and isopropanol as solvent. The Wittig reaction proceeds readily in aprotic solvents with solid bases (KOH, NaOH, K_2CO_3) in the presence of crown ethers (Eq. 6.96)[171,234]:

$$\overset{+}{[}Ph_3P(CH_2)_3OH]\ Cl^- + RC_6H_4CHO \xrightarrow{K_2CO_3/i\text{-}PrOH} RC_6H_4CH{=}CH(CH_2)_2OH \qquad (6.96)$$

R=H, 4-MeO, 2-Cl, 2-F, 4-F, 2-O_2N

Boden reported a solvent effect in alkene stereochemistry when 18-crown-6 complexes of potassium carbonate or potassium *tert*-butoxide were used for ylide formation (Eq. 6.97, Table 6.10)[171]

$$[Ph_3P^+CH_2R]X^- + R'CHO \rightarrow RCH{=}CHR' \qquad (6.97)$$

The reaction of ethyltriphenylphosphonium halides with aldehydes in the presence of potassium carbonate and catalytic amounts of a crown ether in THF affords predominantly *Z* olefins; in dichloromethane *E* olefins are obtained (Table 6.10, Eq.6.97).[171]

Table 6.10. Influence of the solvent on the *Z*:*E* olefin ratio under phase-transfer conditions (Eq. 6.97)[171]

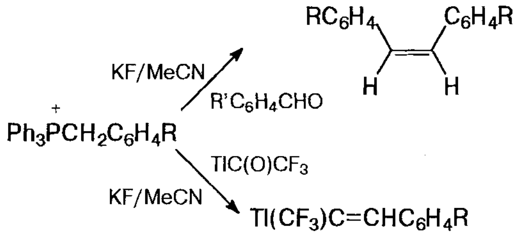
R	R'	Solvent	*Z*:*E* ratio	yield (%)
Ph	Ph	THF	22:78	96
		CH_2Cl_2	30:70	97
Ph	Me	THF	85:15	96
		CH_2Cl_2	22:78	93
Et	Ph	THF	25:75	82
		CH_2Cl_2	46:54	82

Crown ether-catalyzed preparation of alkenes: general procedure (Eq. 6.97)[171]

(a) Benzaldehyde (0.09 mol) and a catalytic amount of 18-crown-6 (0.2 g) were added to a solution of alkylphosphonium salt (0.1 mol) and potassium *tert*-butoxide (0.11 mol) in dichloromethane (500 mL). The reaction mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure and the alkene extracted from the residue with hexane. The alkene was purified by flash-chromatography or vacuum distillation.

(b) A mixture of alkylphosphonium salt (0.1 mol), potassium carbonate (0.1 mol), benzaldehyde (0.09 mol), and a catalytic amount of 18-crown-6 (0.2 g) in dichloromethane (or THF) (250 mL) was heated under reflux for 12–18 h. The mixture was filtered, the solvent was evaporated, and the desired alkene was extracted from the residue with petroleum ether.

In the presence of dibenzo-18-crown-6[234] the reaction between *p*-tolyltrifluoromethylketone and benzyltriphenylphosphonium salts in acetonitrile with excess KF instead of NaOH resulted in olefins in very good yields and stereoselectivity (Table 6.11)[227].



Scheme 6.21

The reaction of substituted benzaldehydes under these conditions proceeds with high *Z* stereoselectivity (Scheme 6.21)[171].

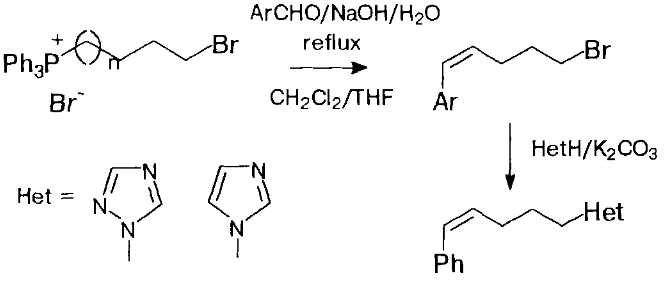
Table 6.11. Wittig reaction in the system KF-CH_3CN (Scheme 6.21)[227]

R	Yield (%)	*Z*:*E* ratio
Ph	100	17:83
4-$O_2NC_6H_4$	88	31:69
α-Thienyl	100	15:85
C_6H_4	100	–
2,5-$(MeO)_2C_6H_3$	88	–

The Wittig Reaction in the system KF–MeCN. General preparation (Scheme 6.21)

A mixture of dibenzo-18-crown-6 (1 mmol) and dried potassium fluoride (200 mmol) in absolute acetonitrile (75 mL) was stirred for 20 min at 70–80°C in an inert atmosphere. *p*-Tolyltrifluoromethylketone (10 mmol), phosphonium salt (10 mmol) (or bis-phosphonium salt (20 mmol) in of acetonitrile (50 mL)) was added and the mixture was stirred for 2 h, filtered, and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel. The yields of olefins are shown in Table 6.11.

ω-Bromoalkenes have been obtained in 72–83% yields and 88-91% *Z* selectivity by means of a solid–liquid-transferred Wittig reaction between ω-bromoalkyltriphenylphosphonium salts and aldehydes[234,236] in THF in the presence of the solid sodium hydroxide. ω-Azolylalkenes were synthesized by N-alkylation and C-alkylation of ω-bromoalkenes, which were obtained by phase-transfer Wittig reaction of ω-bromoalkylphosphonium salts with aldehydes (Scheme 6.22)[235]:



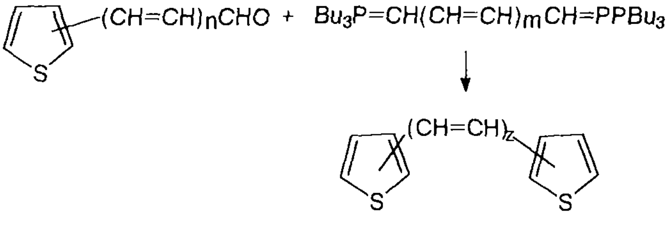
n=2, 4, 6; Ar=Ph, 4-ClC$_6$H$_4$[235,237]

Scheme 6.22

General procedure for the Wittig reaction in the presence of the solid NaOH (Scheme 6.22)[237]

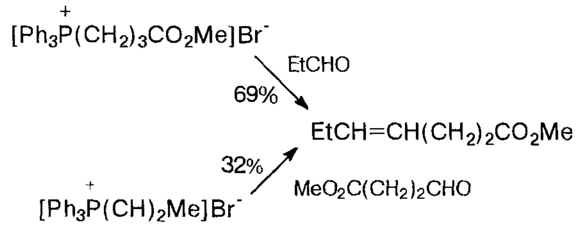
A mixture of a phosphonium salt (44 mmol), a substituted benzaldehyde (40 mmol), sodium hydroxide powder (2 g, 50 mmol), several drops of water, and an organic solvent (100 mL CH$_2$Cl$_2$ or THF) was stirred under reflux for 6–12 h. The product was obtained by filtration and separated by chromatography on a short silica gel column.

Several number of *a*,ω-diethylpolyenes have been prepared by Wittig reaction of aldehydes with appropriate bis-ylides (Scheme 6.23)[238]



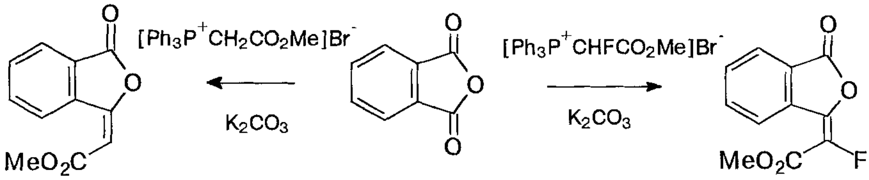
Scheme 6.23

The Wittig reaction of phosphonium salts with cyclic anhydrides under heterogenous solid–liquid phase-transfer conditions in the presence of K$_2$CO$_3$ and LiBr has been proposed as a simple route to enol lactones. The synthesis of methyl *E*-6-nonenoate has been achieved by Wittig reaction under solid–liquid phase-transfer conditions. (Scheme 6.24)[245a]:



Scheme 6.24

Fluoro-substituted enol lactones have been obtained by reaction of cyclic anhydrides with phosphonium salts in the presence of the potassium carbonate and lithium bromide under heterogeneous solid–liquid phase-transfer conditions. (Scheme 6.25)[230,239]



Scheme 6.25

Reaction of carbomethoxymethyltriphenylphosphonium bromide with phthalic, maleic, and succinic anhydrides in the presence of potassium carbonate and lithium bromide proceeds comparatively readily to result in high yields of olefins[226].

General procedure of the Wittig reaction of cyclic anhydrides[240]
Phosphonium salt (2 mmol) and cyclic anhydride (2 mmol) were dissolved in anhydrous THF (30 mL) and anhydrous K_2CO_3 (5 mmol) and LiBr (2 mmol) were added in one portion. The mixture was stirred and heated under reflux for several hours under nitrogen. Ether (20 mL) was added to reaction mixture to precipitate the triphenylphosphine oxide, which was then removed by filtration. The remaining solution was concentrated and the product was purified by flash chromatography on silica gel using petroleum ether, 1:2, as eluent.

Several conjugated dienes have been prepared selectively and in high yield by use of aldehydes of various structures in a two-phase solid–liquid medium.[241] The reaction proceeded when heated under reflux in toluene in the presence of the potassium carbonate (Table 6.12, Eq.98)[226,]:

$$RCHO + Ph_3\overset{+}{P}CH_2CH{=}CH_2]Br^- \xrightarrow{K_2CO_3/\text{toluene}} RCH{=}CHCH{=}CH_2 + Ph_3PO \qquad (6.98)$$

Diene synthesis (Eq. 6.100)
A mixture of propenyltriphenylphosphonium salt (2.5×10^{-2} mol), toluene (20 mL),

aldehyde (2×10^{-2} mol), and potassium carbonate (2.5×10^{-2} mol) was placed in a three-neck flask equipped with a thermometer, condenser, and a mechanical stirrer. The reaction mixture was heated under reflux with stirring. The progress of the reaction was monitored by gas chromatography on a non-polar OV-101 column. At the end of the time indicated in Table 6.12 the mixture was filtered, the solvent was evaporated under reduced pressure, and the residue was extracted with ether to eliminate Ph_3PO. The pure diene was obtained by chromatography on silica gel with hexane–ether as eluent.

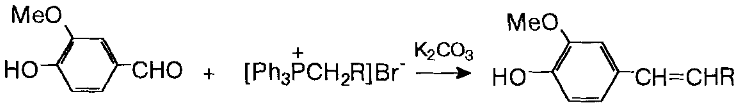
Table 6.12. The Wittig Reaction in a two-phase solid/liquid medium (Eq. 6.98)[226]

R	Time (h)	Yield (%)
Ph	2	95
2-$O_2NC_6H_4$	15	87
2-MeC_6H_4	10	75
4-$MeOC_6H_4$	15	61
$CH_3(CH_2)_5$	5	87
$CH_3CH_2)_9$	5	80

Wittig reaction of fluorine-containing phosphonium salts with aromatic aldehydes in DMFA or THF in the presence of the potassium carbonate gives the corresponding dienes (*Z*:*E* 95:5–17:83) (Eq. 6.99)[241]

$$Ph_3P + BrCF_2CH=CH_2 \longrightarrow Ph_3\overset{+}{P}CH_2CHCF_2Br]Br^- \xrightarrow{K_2CO_3/DMF/ArCHO} ArCH=CHCH=CF_2 \qquad (6.99)$$

Vinyl phenols have been prepared in very good yields in a single-step Wittig reaction. The reaction of the triphenylphosphonium methylide with phenol aldehydes in heterogeneous solid–liquid media require a high-temperature reaction medium but lead to shorter reaction times and better yields than the corresponding reactions with succinic anhydrides (Eq. 6.100, Table 6.13)[242]:



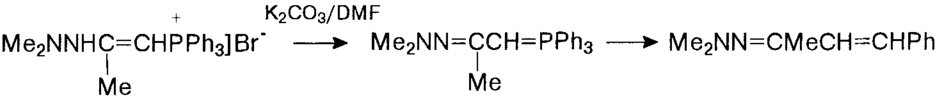
(6.100)

Table 6.13. The preparation of vinyl phenols (Eq. 6.100)

R	Solvent	Temp (°C)	Time (h)	Yield (%)
$CH_3CH_2CH_2$	*i*-PrOH	60	6	90
$CH_3(CH_2)_5$	*i*-PrOH	60	6	80
CH_3	Triglyme	130	6	63

The application of the Wittig reaction under heterogeneous solid–liquid conditions for the synthesis of pheromones, symmetrical and non-symmetrical olefins, deuterated olefins, and various components for high-molecular chemistry has been reviewed by Le Bigot and coworkers[232].

Heterogeneous solid-phase Wittig reaction in the presence of activated alumina has been proposed. Under these conditions the Wittig reaction gives high yields and good stereoselectivity[243]. Palacios and coworkers proposed simple and effective syntheses of *a,β*-unsaturated hydrazone derivatives from ketones (Eq. 6.101)[218]:



$$\mathrm{Me_2NNH}\underset{\mathrm{Me}}{\mathrm{C}}\mathrm{=CH}\overset{+}{\mathrm{P}}\mathrm{Ph_3]Br^-} \xrightarrow{\mathrm{K_2CO_3/DMF}} \mathrm{Me_2NN=}\underset{\mathrm{Me}}{\mathrm{C}}\mathrm{CH=PPh_3} \longrightarrow \mathrm{Me_2NN=CMeCH=CHPh} \qquad (6.101)$$

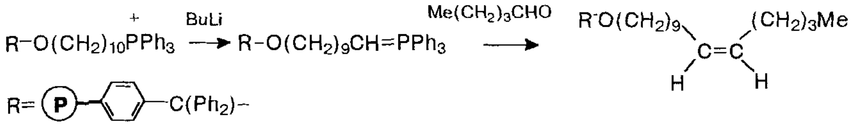
Natural styryl esters of phenolic acids and their analogs have been synthesized by a heterogenous Wittig reaction from (cholesteryloxycarbonylmethyl)triphenylphosphonium bromide and unprotected phenolic aldehydes using K_2CO_3 as base under sonochemical conditions[243b].

6.3.2.3 The Wittig Reaction on Solid Supports

The separation of triphenylphosphine oxide from the olefin product in the Wittig reaction can often be a difficult task. For some years it has been possible to perform some Wittig reactions with cross-linked 4-polystyryldiphenyl-phosphine instead of triphenylphosphine.[239,240,244,245-261] The support is readily prepared by bromination of polystyrene, followed by displacement with lithium diphenylphosphide, and is also commercially available. The polymer-supported Wittig Reaction proceeds well with a variety of substrates, although stereoselectivity suffers if the amount of cross-linking exceeds 2%, and longer reaction times are usually necessary.

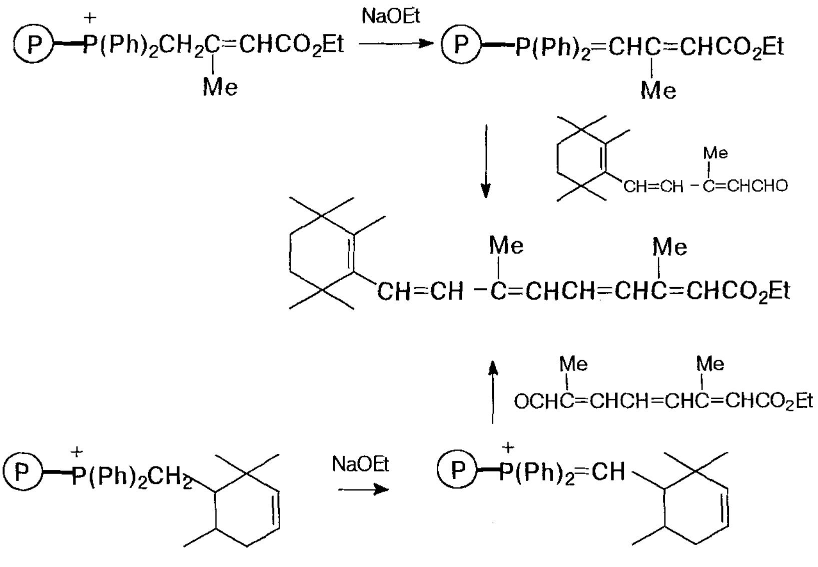
Polymer-supported phosphonium salts have been used to perform the Wittig reaction under heterophasic conditions; these conditions afford good yields of olefins either with saturated aldehydes (formalin, heptanal), or with aromatic aldehydes (substituted benzaldehydes, furfural), and *a,β*-unsaturated aldehydes (cinnamic aldehyde).[246-252]. Phosphonium salts supported on polymer, afford cross-linked phosphorus ylides when treated with base; these ylides undergo different chemical transformations. The application of polymer-supported phosphorus ylides in the Wittig reaction enables the preparation of solutions of practically pure olefins free from phosphine oxide or phosphonium salt impurities, which remain connected to the polymer. The Wittig reaction can be performed in a column filled with polymer-supported phosphorus ylide—a solution of the aldehyde is passed through the column and a solution of appropriate olefin is obtained.

The treatment of polystyrene-supported phosphonium salts with butyllithium enables the synthesis of polymer-supported phosphorus ylides. These ylides react with aldehydes with the formation of olefins with stereoselectivity higher than 90%. This method was used for the preparation of various insect sex-attractants (Eq. 6.102)[246]:



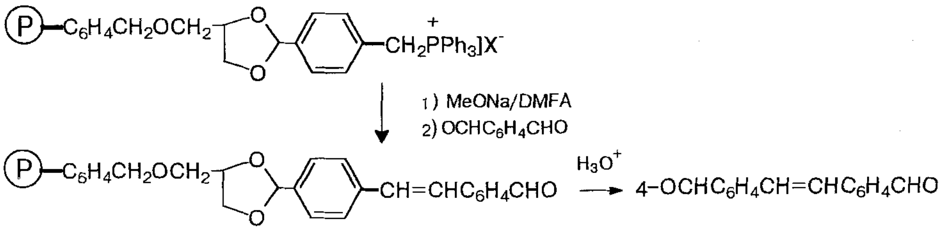
(6.102)

Insoluble 3-ethoxycarbonyl-2-methylallyltriarylphosphonium bromide on microporous styrene polymer is easily dehydrobrominated by sodium ethylate in ethanol with the formation of a polymer-supported ylide. On treatment of the ylide with aldehyde ethyl retinoates were obtained in 55–70% yield in the form of the *Z* and *E* isomers (Scheme 6.26).[247]



Scheme 6.26

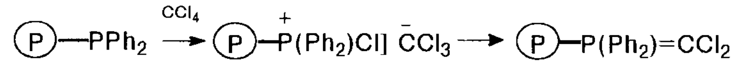
P-Ylides reacts smoothly with resin-bound aldehydes and ketones to provide alkenes in good yield and excellent stereoselectivity and purity[239c,248]. 11-Hydroxyundecene-triphenylphosphonium bromide supported on polystyrene was deprotonated by ylide which reacted with propionaldehyde in THF to afford a 93:7 mixture of *Z* and *E* isomers of 14-hydroxytetradecene-3 in 84% yield[249].



Scheme 6.27

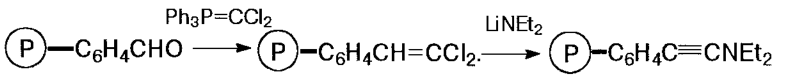
After treatment with sodium methylate in DMFA phosphonium salts supported on polystyrene afforded phosphorus ylides immobilized to polymer which were used in the synthesis of dialdehydes, as shown on Scheme 6.27[250]:

Dichloromethylides supported on polystyrene have been obtained by carbon tetrachloride-treatment of phosphines immobilized on a polymer carrier (Eq. 6.105) [251]

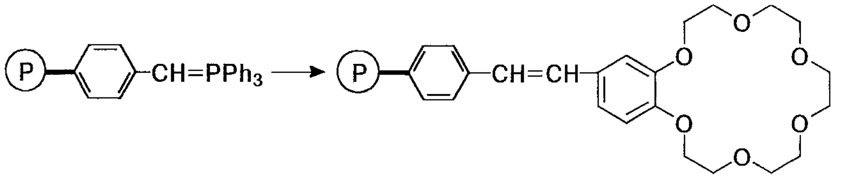


$$\text{Ⓟ}-PPh_2 \xrightarrow{CCl_4} \text{Ⓟ}-\overset{+}{P}(Ph_2)Cl]\ \overset{-}{C}Cl_3 \longrightarrow \text{Ⓟ}-P(Ph_2)=CCl_2 \qquad (6.103)$$

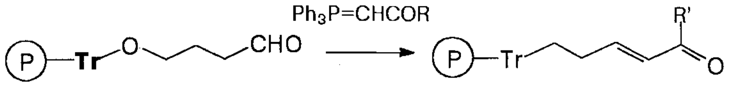
The Wittig reaction has been used to modify polymeric reagents, for instance for the preparation of insoluble polymeric inamines (Eq. 6.104)[254,255] or for the preparation of polymer supported crown ethers (Eq. 6.105)[256]. Functionalization of polymer was successfully achieved by Wittig reaction of β-ketoylide with cross-linked aldehyde, after preliminary saturation of the polymer with THF (Eq. 6.106)[256]:



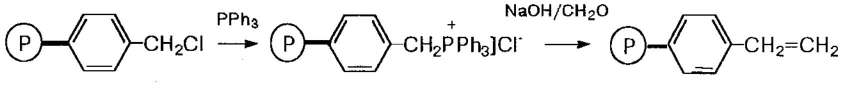
$$\text{Ⓟ}-C_6H_4CHO \xrightarrow{Ph_3P=CCl_2} \text{Ⓟ}-C_6H_4CH=CCl_2 \xrightarrow{LiNEt_2} \text{Ⓟ}-C_6H_4C\equiv CNEt_2 \qquad (6.104)$$



(6.105)



(6.106)

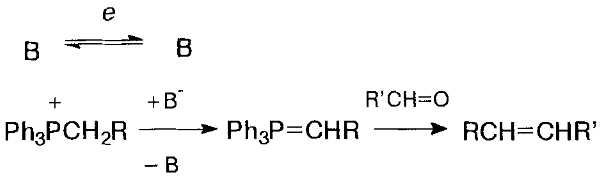


(6.107)

Wu Yumin and coworkers reported the synthesis of several types of polymer-supported phosphonium salt and their use in the Wittig reaction with aldehydes (Eq. 6.107)[258]. Polymer-supported compounds containing lignin have been synthesized by Wittig reaction of chloromethylated polystyrene bearing cross-linked aldehyde groups[259]. Rotella developed a method for the solid-phase synthesis of olefins and hydroxyethylene peptidomimetics[261a] A polymer-supported Wittig reaction has been performed with ylides containing two α-hydrogen-linked carbon atoms[260]. A review dedicated to polymer-supported Wittig reactions has recently been published in the Russian literature[261].

6.3.2.4 The Electrochemical Method

In recent years an electrochemical method has been developed for the synthesis of phosphorus ylides from phosphonium salts (see Section 2.2.1.4).[262-264] Shono and Minami have electrolyzed phosphonium salts in the presence of aldehydes and obtained olefins in good yields[262a]. Saveant and Binh showed that ylides are formed by the electrolytic reduction of a variety of phosphonium salts under aprotic conditions. Phosphorus ylides prepared from benzyl-, cinnamyl-, and polyenylphosphonium salts have been detected by cyclic voltammetry[262]. The greatest potential for the synthesis the phosphorus ylides by this method is use of pro-bases which afford an anion on electrochemical reduction. The latter deprotonates the phosphonium salt with the formation of the phosphorus ylide (Scheme 6.28)[263];



$$B \xrightleftharpoons{e} B$$

$$Ph_3\overset{+}{P}CH_2R \xrightarrow[-B]{+B^-} Ph_3P{=}CHR \xrightarrow{R'CH{=}O} RCH{=}CHR'$$

Scheme 6.28

The dianion of azobenzene generated by cathode reduction in aprotic solvents readily converts benzyltriphenylphosphonium salts into ylides which then undergo the Wittig reaction with benzaldehyde to furnish stilbene.

Utley and coworkers[263] proposed a 9-fluorenemethylene derivative as a pro-base which on electrochemical reduction in dimethylformamide forms dianions with strong basic properties which readily convert various phosphonium salts into phosphorus ylides.

The advantages of electrochemical method for the Wittig reaction are good reproducibility of the reaction conditions, possibility of controlling the course of the reaction by changing the electric current, and the effect of changing the reaction conditions on the stereochemistry of the Wittig reaction.

The electrogeneration of dianions from derivatives of 9-fluorenmethylene used as pro-base results in conversion of benzyltriphenylphosphonium nitrite to stilbene in 94% yield (*E*:*Z* isomer ratio = 96:4), and to 1.4-diphenylbutadiene in 67% yield. The acetate of vitamin A was synthesized in 40% yield and with stereochemical purity of the 11-*cis*-isomer of 76%.

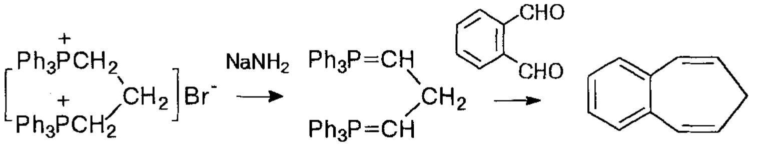
Collignon[264] reported magnesium activation of the electrochemical Wittig reaction. The electrochemical reduction of phosphonium salt between a carbon-felt cathode and a sacrificial Mg anode in DMF led to P-ylide which was reacted with aliphatic aldehydes to give *gem*-difluoroalkenes in good yield.

6.4. Application of the Wittig Reaction

The Wittig reaction is widely used in organic synthesis, particularly in the synthesis of natural products The great advantages of the Wittig reaction is its high regio- and stereoselectivity, the possibility of olefinating carbonyl compounds without rearrangements and isomerization, and the accessibility of starting compounds. The Wittig reaction has been used to prepare pharmaceutical products (prostaglandins and leukotrienes), pheromones, insect sex-attractants, various hormonal substances, vitamins, food additives, and pigments etc[265]. Various cyclizations have been performed by means of Wittig reactions[266]. The reaction is used in the industrial production of vitamin A, carotenoids, and various aromatic and medical products. The volume of vitamin A produced by BASF is more 600000 kg year^{-1} (see Section 2.3.4).

6.4.1 Cyclic Compounds

The Wittig reaction is a convenient method for the synthesis of cyclic systems. The first example of the synthesis of cyclic compounds by the Wittig reaction was reported by Wittig, who described the synthesis of 3,4-benzocyclo-heptatriene by reaction of *o*-phthalic aldehyde with a diylide synthesized from 1,3-bis (triphenylphosphonium) propane dibromide (Eq. 6.108) [267]:



(6.108)

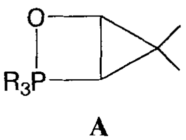
Syntheses of cyclic compounds by Wittig reactions have been described in several articles, including reviews[265–276].

There are two approaches to the synthesis of cyclic compounds by the Wittig reaction:

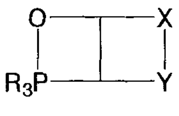
1 - intramolecular cyclization of monofunctional ylides bearing a carbonyl group in the ω position; and
2 - Wittig reaction of bifunctional ylides with bifunctional carbonyl compounds (bis Wittig reaction).

6.4.1.1 The Intramolecular Wittig Reaction

The intramolecular Wittig reaction is a powerful method for the synthesis of heterocyclic systems[273-277]. This reaction enables the preparation of rings containing more than four atoms—3- and 4-membered cyclic systems are not accessible by this methodology because of the highly strained bicyclic oxaphosphetane intermediates **A** and **B** which must be formed during this reaction.[277]



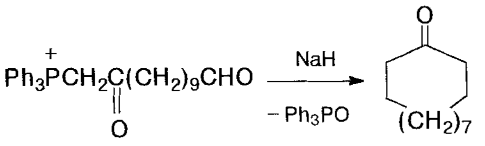
A



B

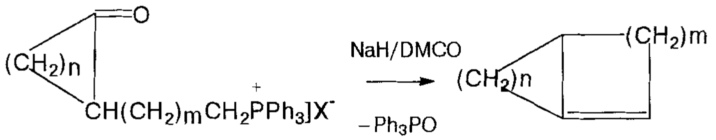
Carbocyclic Compounds

The treatment with base of phosphonium salts with a carbonyl group in the in ω position leads to the formation of the corresponding ylide. This is followed by intramolecular nucleophilic attack of the ylide carbon atom on the carbonyl carbon accompanied by elimination of the triphenylphosphine oxide and the formation of an unsaturated cyclic compound (Eq. 6.109)[269-296]:



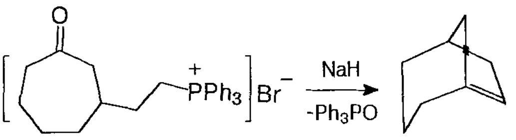
(6.109)

The treatment of keto-phosphonium salts with sodium hydride in dimethyl sulfoxide affords cyclopentene or cyclohexene derivatives in yields of 50–66% (Eq. 6.110)[269]:



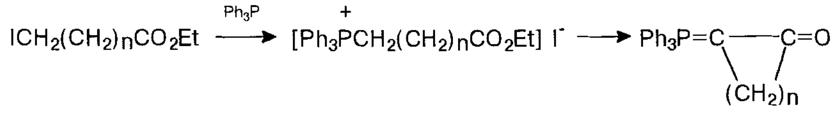
(6.110)

The intramolecular Wittig reaction enables the preparation of cyclic alkenes in which the position of the double bond in ring is strictly defined, as, for instance, in the synthesis of the macrocyclic diarylheptanoid garugamblin-2[270] or bicyclo[4,2,1] nonene-1[271] (Eq. 6.111):



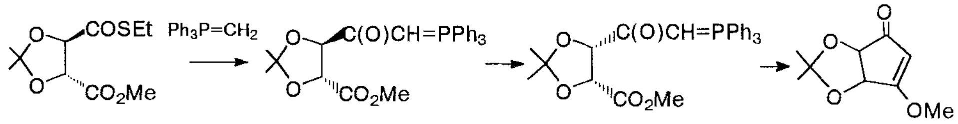
(6.111)

ω-Ethoxycarbonylphosphonium salts, prepared by reaction of triphenyl-phosphine with ω-iodocarbonic acid esters furnish, on treatment with base, the corresponding ω-ethoxycarbonylalkylphosphorus ylides; on intramolecular acylation these are converted into cyclic α-ketoylides (n = 3–5) (Eq. 6.112)[278]:



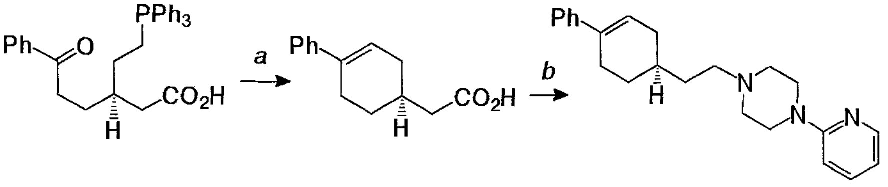
(6.112)

Five-membered hydroxycyclopentane cycles, structural fragments of prostaglandins, have been prepared by intramolecular Wittig reaction. The synthesis of optically active cyclopentenes has been developed on the basis of *R,R*-tartaric acid monothioester as chiral auxiliary. In the first step of the reaction the thioether was acylated with triphenylphosphonium methylide and in the second step the acylide was converted into acetonide 4*R*,5*S*-dihydroxy-3-methoxy-2-cyclopentenone by intramolecular Wittig reaction[280]. The pentenone was then used for the preparation of prostaglandins (Eq. 6.113)



(6.113)

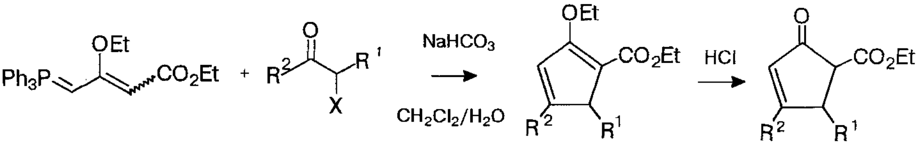
Johnson and coworkers described the syntheses of chiral 4-substituted 1-phenylcyclohexane PD 137789 by intramolecular Wittig reaction The *S*-4-substituted 1-phenylcyclohexene, which, unlike its enantiomer, has dopamine agonist properties, has been synthesized by an intramolecular Wittig reaction (Scheme 6.29)[296]



a=NaH/DMSO; BuOCOCl/Et3N, 2-Py-pyperidine

Scheme 6.29

Allylylides have two nucleophilic centers and react with various electrophiles at either the *a* or *γ* position depending on the electrophile and the substituents on the phosphorus ylide (Eq. 6.114–6.116). Thus the [3+2]-annulation reaction of allylylides with *a*-halocarbonyl compounds under mild conditions leads to the regioselective formation of cyclopentadienes **19**,**20** with a variety of substituents (Eq. 6.114, Table 6.14)[282a]:

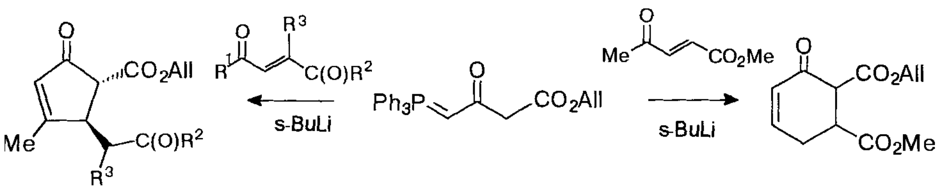


19 **20** (6.114)

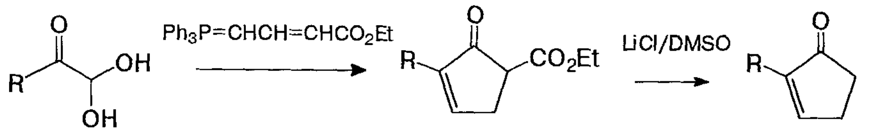
Hatanaka and coworkers[281,282] reported a very efficient approach to substituted five- nd six-membered carbocycles. The reaction also occurs if lithium perchlorate is used as the base (Eq. 6.115). These authors proposed a short-step synthesis of substituted cyclopentenone derivatives by reaction of triphenylphosphonium *β*-alkoxycarbonyl-2-oxopropylide with 1,2-diacylethylenes.[111b,282] and a one-step synthesis of functionalized fulvenes.[282c,d] Hydroxycyclopentenones have been obtained from the reaction of 3-ethoxycarbonyl-2-oxo-propylidenetriphenylphosphorane with glyoxals (Eq. 6.116).[282e]

Table 6.14. The reaction of allylylides with α-haloketones (Eq. 6.114)[281,282]

R^1	R^2	Yield of **19** (%)	Yield of **20**(%)
Ph	H	92	99
Me	H	84	91
C_5H_{11}	H	81	98
$Cl(CH_2)_3$	H	86	92
Et	Me	57	98
EtS	H	72	98



R= Me, Ph; R^2=EtO, EtS, Ph; R^3=CO_2Et, H (6.115)

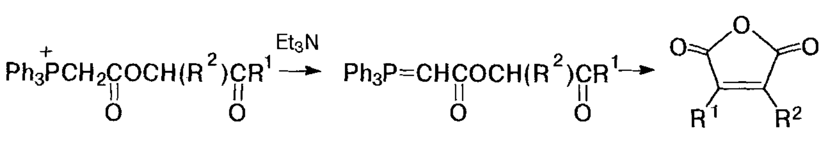


(6.116)

Various oxygen-, nitrogen-, and sulfur-containing heterocycles can be prepared by intramolecular Wittig reaction. An excellent review by Zbiral[275] was published in 1974 and short review by Hiron in 1995[277].

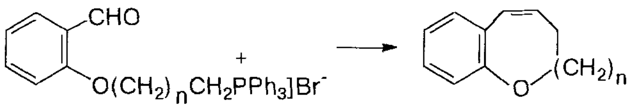
Heterocycles Containing Oxygen

Oxygen-containing heterocycles have been obtained by intramolecular Wittig reaction of phosphorus ylides with side-chains containing ester or carbonyl groups. Thus, triphenylphosphonium acetate *a*-hydroxyketones were converted into butenolides by action of triethylamine in dichloromethane solution (Eq. 6.117)[284-301]:



(6.117)

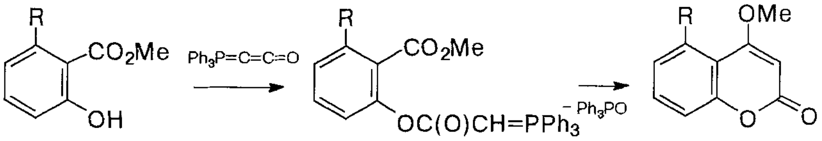
O-(alkoxytriphenylphosphonium)benzaldehyde readily cyclizes upon treatment with lithium alkoxide with the formation of a seven-membered dihydroxybenzoxepine ring when $n = 2$ and eight-membered dihydrobenzoxocine ring when $n = 3$. The reaction also furnishes some rearranged products, the yields of which can be strongly reduced by variation of the reaction conditions. Aldehyde phosphonium salts containing one methyl group in the side-chain furnish 2H-chromenes on treatment with alcoholate (Eq. 6.118)[286–290]:



R=Me, Et, n=1-3

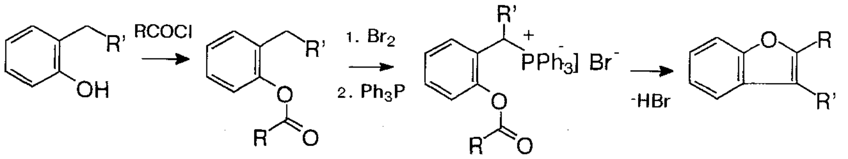
(6.118)

Ylides formed as a result of addition of salicylic acid esters to triphenylphosphonium ketenylide, enter into an intramolecular Wittig reaction with the formation of coumarin or pyrane derivatives (Eq. 6.119)[291,301]:



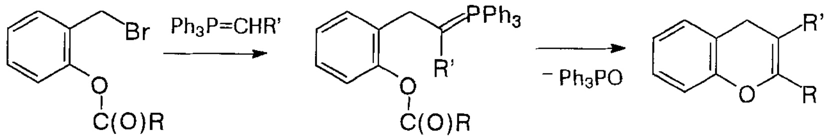
(6.119)

Ylides with two or three methylene groups in the side-chain cyclize analogously with the formation of appropriate enol esters of dihydrofuran or dihydropyran. Le Corre and coworkers have obtained phosphonium salts by consecutive etherification, bromination, and quaternization of triphenylphosphine (Eq. 6.120). Treatment of phosphonium salts with sodium *tert*-amylate led to the formation of benzofurans in high yields (72–94%)[292]. Le Corre also synthesized chromenes (yields 68–98%) and isochromenes (yields 50–80%) by this method (Eq. 6.121,122)[289,290,293,294].

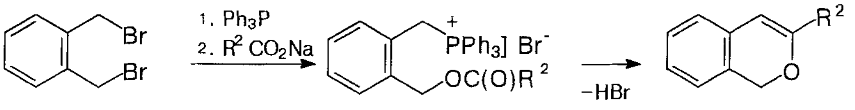


R=Alk, Ar; R'=H

(6.120)



(6.121)

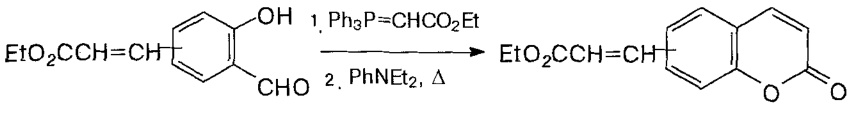


(6.122)

R=Me, Et, Ph; R' =C(O)Me, CO2Et, Ph; R^2=H, Me

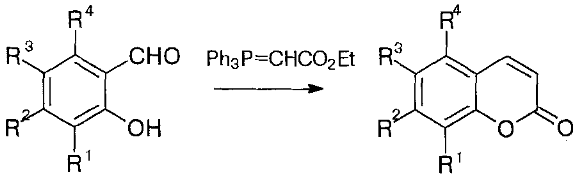
Coumarins

The Wittig reaction is a convenient method for the synthesis of coumarine derivatives.[295-314] Thus the Wittig reaction of triphenylphosphonium carboethoxy-methylide with 3-nitrosalicylaldehyde gave coumarin derivatives (Eq. 6.123)[295]:



(6.123)

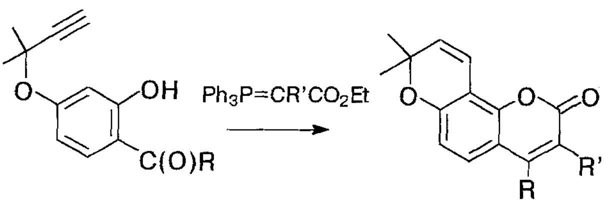
Mononitrosalicylaldehydes react with triphenylphosphonium carboethoxy-methylide in Et_2NPh or Ph_2O at 210°C in the absence of solvent to give predominantly the expected coumarins (Eq. 6.124)[307,308]:



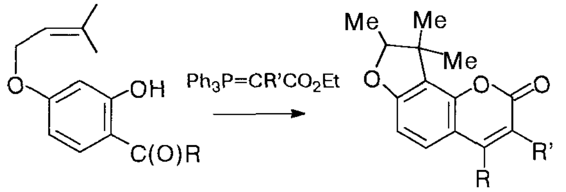
(6.124)

R^1	R^2	R^3	R^4	Yield(%)
O_2N	H	H	H	35
H	NO_2	H	H	32
H	H	NO_2	H	43
H	H	H	NO_2	55

Nicolaides et al.[306] and Litinas et al.[310] described the synthesis of coumarin-7,8 derivatives fused on to furan, pyran, and dioxol rings by reaction of stabilized and semi-stabilized ylides with 4-methylchromene-2,7,8-trione (Eq. 6.125).



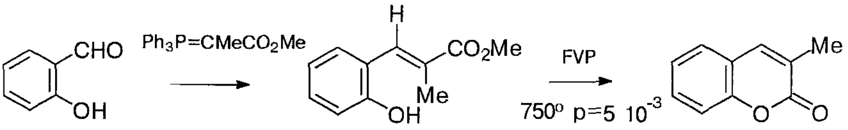
(6.125)



(6.126)

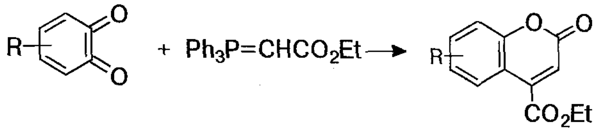
Seselin[316] and others have described the preparation of related pyran, furocoumarin, and 2′,3′,3″-dihydroangelicine derivatives[297] with dopamine agonist properties by Wittig reaction of appropriate unsaturated ethers and by a tandem Clausen rearrangement (Eq. 6.126)[299]:

Synthesis of coumarin derivatives in high yield by FVP of 3-(2-hydroxyaryl)propenoic esters was realized by Cartwright and McNab (Eq. 6.127)[314b]:

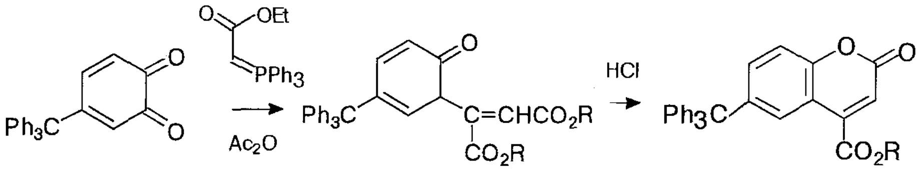


(6.127)

A variety of examples of the Wittig reaction of stabilized phosphorus ylides with 1,4-naphthoquinone, and 1,2- and 1,4-benzoquinones were described by Boulos[312a–c] and Nicolaides et al.[313] Reaction of triphenylphosphonium alkoxycarbonylmethylide with 4-triphenylmethyl-1,2-benzoquinone and with substituted 2-amino-1,4-naphthoquinone was studied by Osman (Eq. 6.128)[68,314a]. The Wittig reaction of $Ph_3P{=}CHCO_2R$ with 4-triphenylmethyl-1,2-benzoquinone proceeds in acetic anhydride at room temperature with the formation of fumarates; these can be converted into coumarins by treatment with hydrochloric acid (Eq. 6.129)[314]:

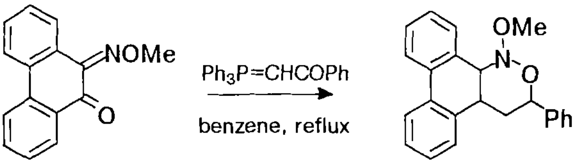


(6.128)



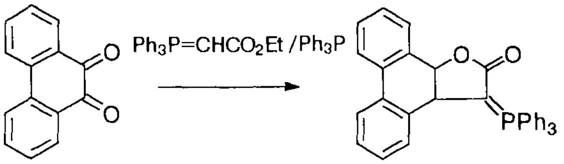
(6.129)

The reaction of the 10-(methoxyimino)phenanthro-9-one with phenacylide in boiling benzene leads to the formation of methoxy-1H-phenantro-[9,10*c*](1,2)-oxazine, which was then converted into a triphenylenedicarboxylic acid derivative (Eq. 6.130)[302,303]:



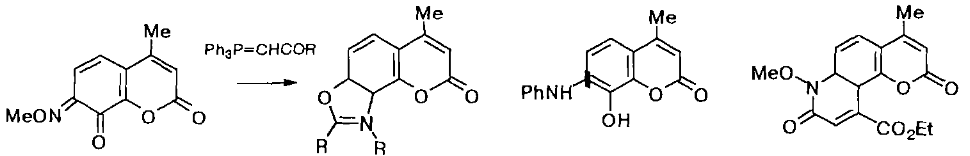
(6.130)

Nicolaides and Litinas proposed methods for the synthesis of coumarin derivatives by reaction of *ortho*-quinones and *ortho*-quinoneimines with P-ylides[300-304,306,311]. The reactions of triphenylphosphonium ethoxycarbonylmethylide with certain *ortho*-quinones in the presence of triphenylphosphine, alkanol, acetic anhydride leads to the formation of new phosphorus ylides (Eq. 6.131):[300]



(6.131)

Under phase-transfer conditions benzylides and ester- and keto-stabilized ylides react with 7-(methoxyimino)-4-methyl-2*H*-chromene-2,8(7*H*)-diene to give benzopyranooxazo-1,8-ones or pyridones, depending on the ylide used[302]. The reaction of **15** with stable P-ylides gave benzopyranooxazoles **16** (R = Bz, CO_2Me, CO_2Et) and **17**. (Scheme 6.30)



15

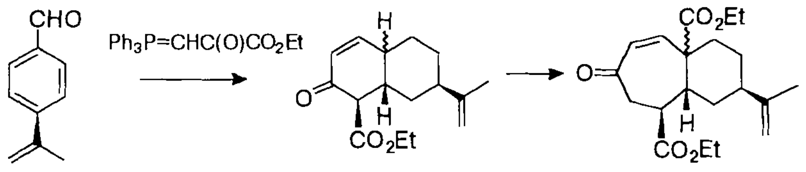
R=Me, Ph

16

17

Scheme 6.30

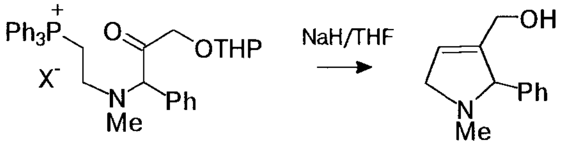
Annulation of *R*-perillaldehyde with an ylide gives a cyclohexenone which if subjected to a Beckwill–Dowd ring-expansion sequence yields the corresponding cycloheptenone derivatives (Eq. 6.132)[305]



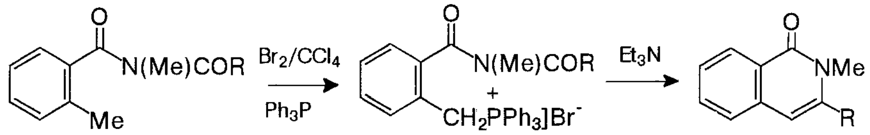
(6.132)

Heterocycles Containing Nitrogen

Various methods based on the Wittig intramolecular condensation have been developed for the preparation of four- and five-membered rings containing nitrogen.[315-329] For instance, the intramolecular Wittig reaction have been used or the synthesis of *N*-alkyl-3-pyrrolines (Eq. 6.135).[320] 2-methyl-3-(aryl/alkyl)-1-oxo-1,2-dihydroisoquinolones have been prepared in 69–88% yield by a one-pot synthesis from the amides **18** (Eq. 6.136).[315a,315b] Compounds **18** were prepared by sequential acylation of 2-$MeC_6H_4CONHMe$ with RCOCl, photochemical bromination, and reaction of the resulting 2-$(BrCH_2)C_6H_4CON(Me)COR$ with triphenylphosphine.[346]



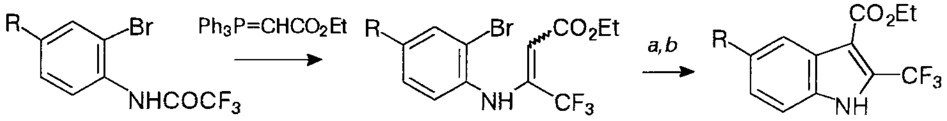
(6.135)



18

(6.136)

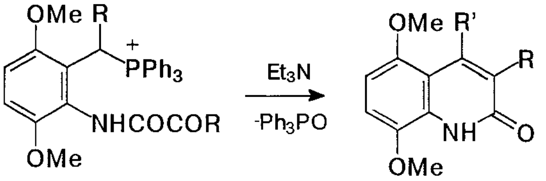
Anilides undergo a Wittig reaction with P-ylides to yield the corresponding enamine derivatives; these react under Heck condensation to give indoles and quinolones (Eq. 6.133)[316].



a=$NaHCO_3$, $Pd(OAc)_2/PPh_3$; *b*=DMF

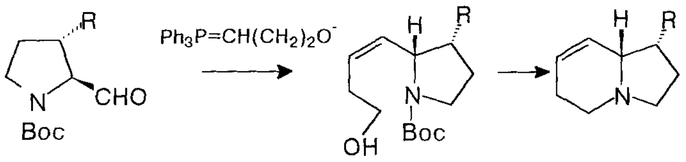
(6.133)

5,8-Dimethoxy-2(1*H*)-quinolines, which are key intermediates of antitumor diazaquinomycin A analogs, were obtained by intramolecular Wittig reaction in the presence of triethylamine (Eq. 6.134)[317]:



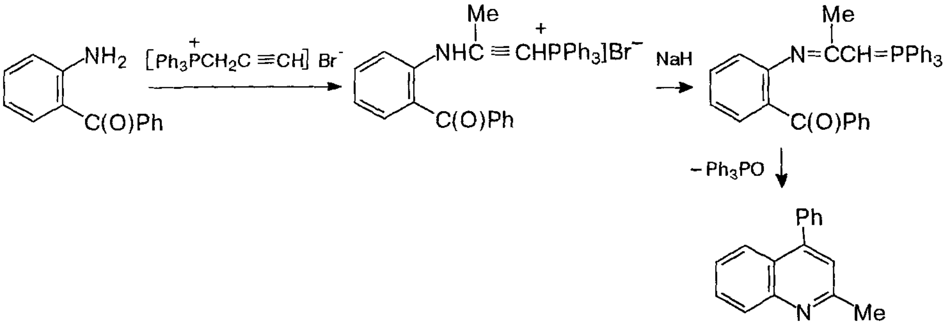
(6.134)

3-Hydroxypropylphosphonium ylide has been used as a 3-carbon synthon to construct a 6-membered ring in a new enantio-controlled synthesis of indolizidine alkaloids from prolinals (Eq. 6.137)[319]:



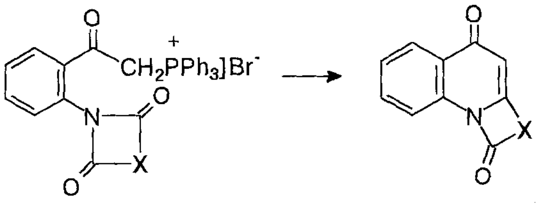
(6.137)

Propargyltriphenylphosphonium bromide adds *o*-aminobenzophenone with the formation of the vinylphosphonium salt. Reaction of this with sodium hydride in acetonitrile affords the ketoylide which is converted by intramolecular Wittig cyclization into 2-methyl-4-phenyl-quinoline (Scheme 6.31)[318]:



Scheme 6.31

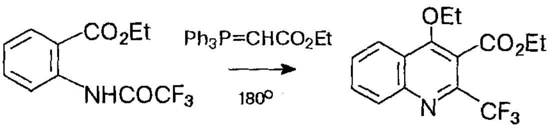
The intramolecular Wittig reaction on substituted aminoacetophenones has been used for the synthesis of novel quinoline derivatives (Eq. 6.138)[330]:



(6.138)

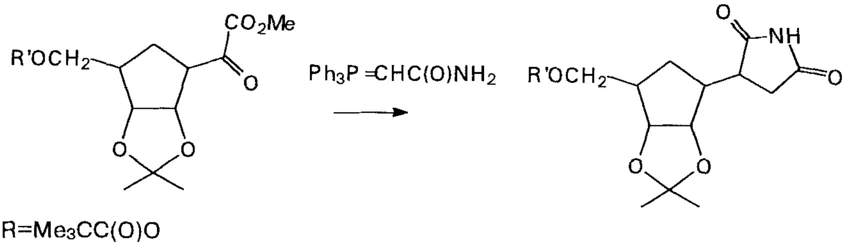
X=CH2CH2, 1.4-C6H4

N-Trifluoroacetanilide undergoes Wittig reactions to give enamine derivatives which are precursors to indoles and quinolines (Eq. 6.139)[316,321]:



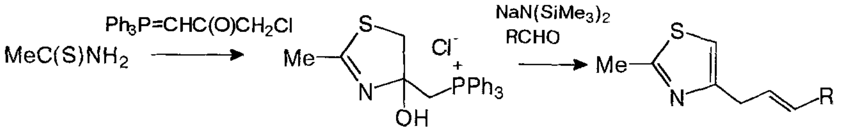
(6.139)

The first enantioselective synthesis of a carboxylic analog of showdomycin was accomplished in five steps from unsaturated ester via a Wittig reaction in a key step and asymmetric Diels-Alder reaction (Eq. 6.140)[322]:



(6.140)

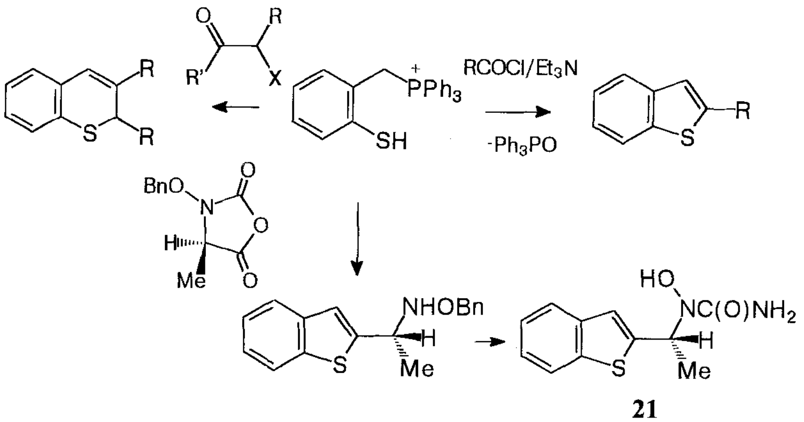
Williams and coworkers described an efficient approach for the preparation of thiazolylmethylphosphonium salts (Eq. 6.143)[283]:



(6.141)

Heterocycles Containing Sulfur

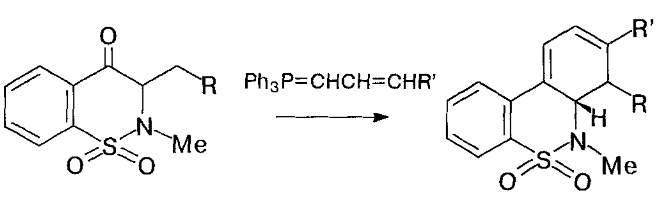
Methods have been developed for the synthesis of five- and six-membered heterocycles containing sulfur by means of intramolecular Wittig reactions[277,303,323-330]. Thus benzo[*b*]thiophenes and 2*H*[1]benzothiopyran derivatives were synthesized in good yields from 2-mercaptophenyl-methyltriphenylphosphonium bromide (Scheme 6.32)[323] and (2-mercaptophenyl)methyltriphenylphosphonium bromide has been used to form the benzo[*b*]thiophene ring of zileuton™ **21**, a potent inhibitor of 5-lipoxygenase[277,323].



21

Scheme 6.32

Dalla Croce and La Rosa reported that 1,2-benzothiazin-4-one-1,1-dioxides undergo intramolecular Wittig condensation to give the heteropolycyclic system **22** (Eq. 6.142)[298]:



22

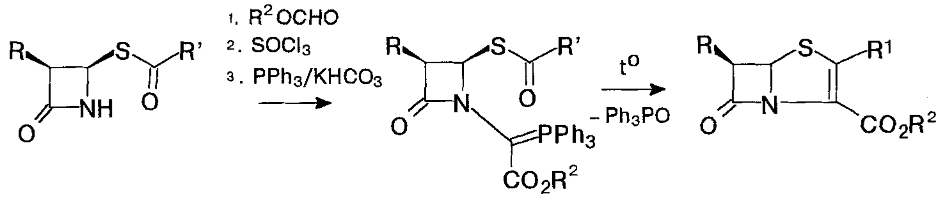
(6.142)

R	R'	Yield of **22**,%
Me	CO_2Me	31
Me	CN	76
Ph	Ph	52
Ph	Me	87

β-Lactam Antibiotics

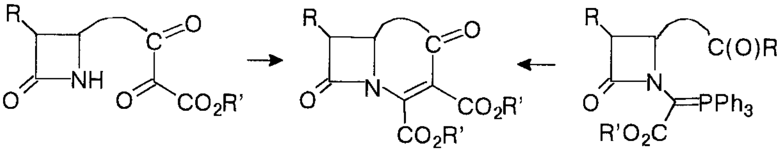
Intramolecular Wittig reactions have found numerous applications in the synthesis of *β*-lactam antibiotics, carbapenems, cephems, and carbacephems, which are structural hybrids of penicillin and cephalosporin derivatives of 1-carbodithiacepheme and 1-oxa-1-dithiacepheme acids[90,324-349].

Woodward and coworkers developed methods for the synthesis of *β*-lactam antibiotics and in 1978 published the first report on this topic[324]. 4-Thioacetylasetidinone was converted into a stabilized ylide, cyclization of which upon heating in toluene gave the penemate (Scheme 6.33, Table 6.15)[324-328]. Some preparative details of this synthesis are generalized in Table 6.15. The synthesis of penem derivatives by intramolecular Wittig reaction between ylide and thiol esters were reviewed by Nagano.[329]



Scheme 6.33

Most asymmetric syntheses of bicyclic *β*-lactams antibiotics begins with construction of an optically active monocyclic *β*-lactam. To form the second ring of penems, carbopenems, cephems, and carbocephems, two different, but complementary methods have been used most frequently—a carbene insertion developed by the Merck group and an intramolecular Wittig reaction devised by Woodward (Scheme 6.34):

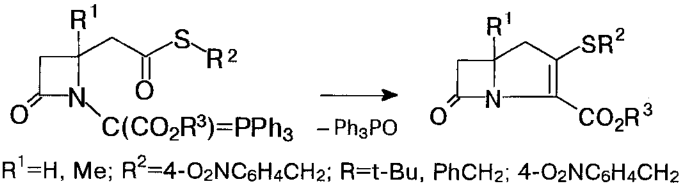


Scheme 6.34

Table 6.15. Syntheses of penemates (Scheme 6.33)[324]

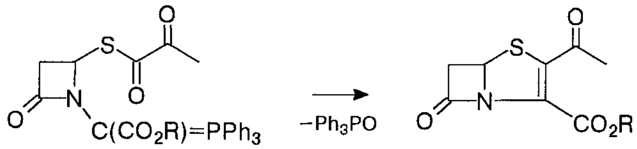
R^1	R^2	Temp. °C	Time,h	Yields,%
Me	t-Bu	111°C	10	70
i-Pr	t-Bu	80-100	8	6
Ph	$4\text{-}O_2NC_6H_4CH_2$	90	3	53
$4\text{-}O_2NC_6H_4$	t-Bu	55	17	90
Me	Me	80	46	57
Me	$4\text{-}O_2NC_6H_4CH_2$	80	4-5	70
Me	CH_2CCl_3	80-100	3	10

Ponsford and coworkers synthesized of carbapenemates in satisfactory yields (Eq. 6.143)[331]:



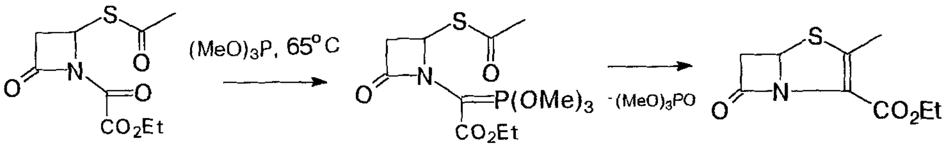
(6.143)

Intramolecular cyclization in a sequence of β-lactams preferentially leads to the formation of five-membered, but not of six-membered rings, i.e. cyclization of the ylide as a result of attack of the ylide carbon on the thioester led to the formation of five-membered rings, although the formation of six-membered is possible (Eq. 6.144)[328]:

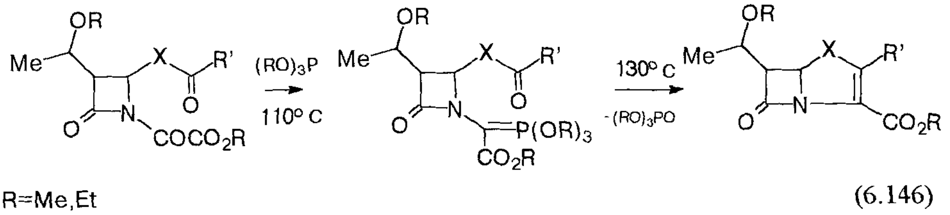


(6.144)

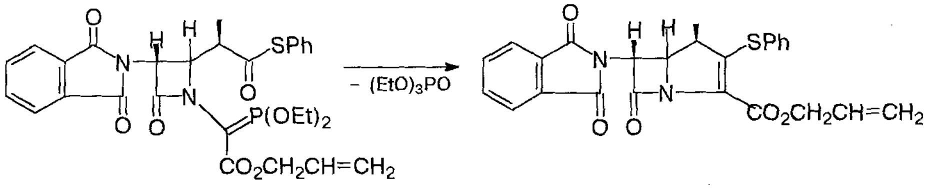
Intramolecular cyclization with the formation of β-lactams was also realized by means of trialkoxyphosphonium ylides (Eq. 6.145,146)[332,333]. Derivatives of 6-acylamino- and 6-phthalimido-1-methylcarbopeneme were obtained in approximately 60% yields by heating triethoxyphosphonium ylides in xylene (Eq. 6.147)[340]:



(6.145)

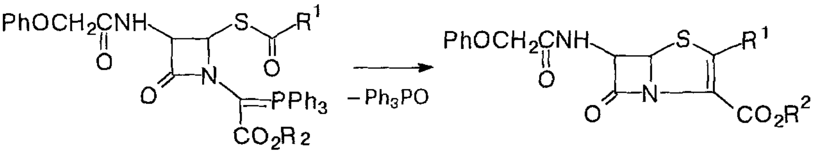


(6.146)



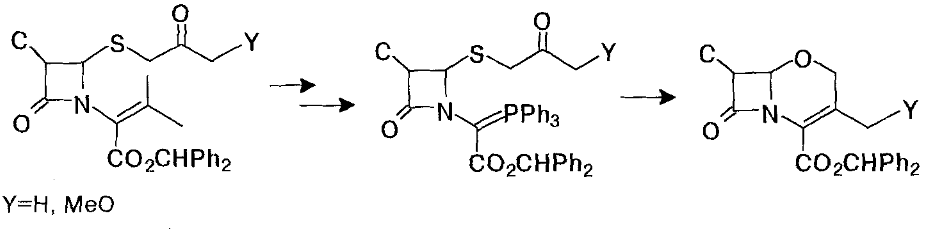
(6.147)

Construction of the penem acid skeleton was achieved by intramolecular cyclization of the ylide function with the carbonyl function of thioester groups[324,335]. This cyclization was applied to several substituted thioazetidinones (Eq. 6.148)[331,336,337]:



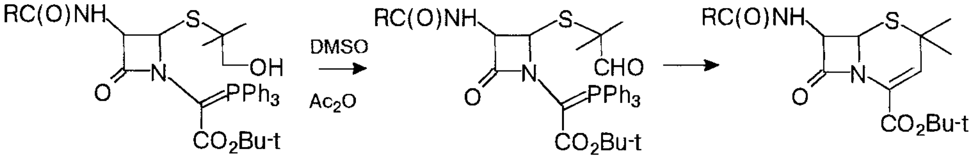
(6.148)

Derivatives of β-acetonyloxyazetidinone were ozonized, then reduced, chlorinated, and treated with triphenylphosphine, to furnish ylides in good yields. Upon heating the ylides cyclize smoothly with the formation of 1-oxacephame derivatives. The authors suppose that this cyclization scheme can be applied for the industrial preparation of 7α-methoxy-1-oxacefemates (Scheme 6.35)[323]



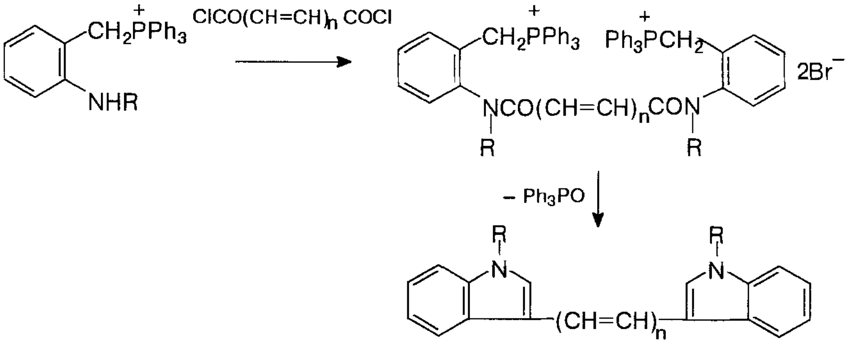
Scheme 6.35

Esters of 2,2-dimethyl-3-cephem-4-carbonic acid have been obtained by intramolecular cyclization of an ylide. The aldehyde function generated by oxidation of OH groups by the method of Kornblume (Scheme 6.36)[338]:



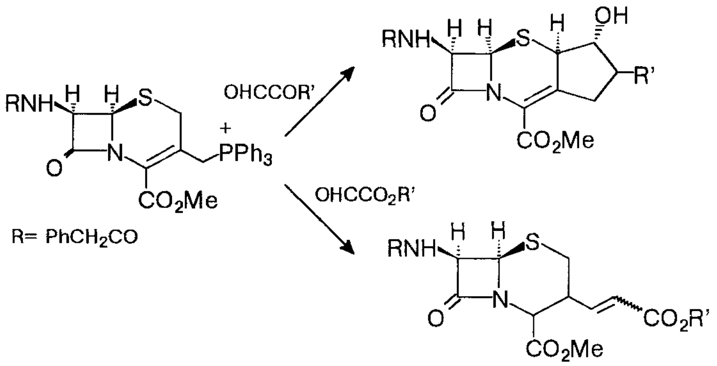
Scheme 6.36

The intramolecular Wittig reaction of bis(benzyltriphenylphosphonium) bromide leads to 2,2-diindoles when *n*= 0 and to 1,2-diindolylethylenes when *n* = 1 (Scheme 6.37)[339]:



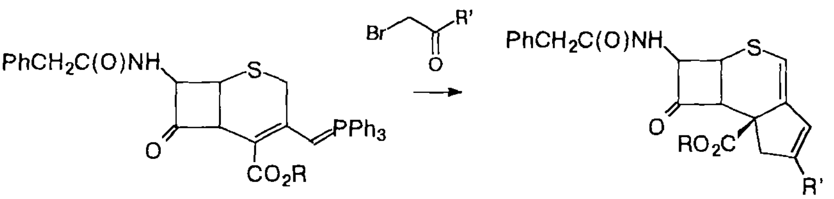
Scheme 6.37

Cephalosporin phosphorus ylides react with bifunctional carbonyl compounds to provide 3-alkenylcephemes and new tricyclic derivatives (Eq. 6.149)[340]. Several novel cephalosporins and cephem derivatives with substituted-vinyl C-3 functionality have been synthesized via Wittig reaction of the appropriate cephalosporin phosphonium ylides (Scheme 6.38)[342,344a,b].



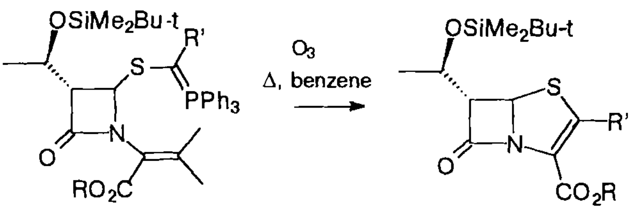
Scheme 6.38

2-Amino-3-vinyl-3-cephem-4-carboxylic acid was prepared via Wittig reaction of cephem derivatives[345]. The reaction of cephalosporin 3′-triphenylphosphonium ylide with haloketones has been used to synthesize new tricyclic cephalosporins. (Eq. 6.150)[345]:



(6.150)

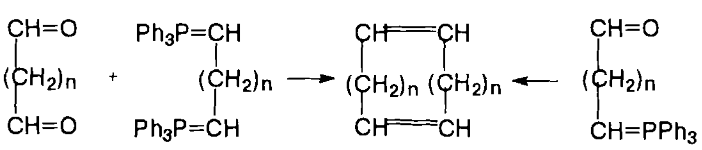
Chaterjee and co-workers have described the preparation of 2,3-disubstituted 4,5-dihydrothiophenes and thiophenes by intramolecular non-classical Wittig reaction of thiolcarboxylates[346]. An alternative intramolecular Wittig route to penams involving ylides has been reported. The ylides are prepared by the reaction of both stabilized and unstabilized ylides with β-lactam disulfide. The method has been applied to the keto analog thus avoiding the ozonolysis step (Eq. 6.151)[347,348]. Barker and colleagues described a brief and efficient synthesis of *L*-substituted 6-(1*R*-hydroxyethyl)penems[349].



(6.151)

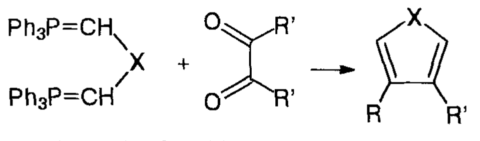
6.4.1.2 The bis-Wittig Reaction

The double Wittig reaction of dicarbonyl compounds with bis-ylides is a widespread method for the synthesis of the cyclic dienes. The latter compounds can also be prepared by dimerization of ω-carbonyl-substituted phosphorus ylides (Eq. 6.152):[350-373]



(152)

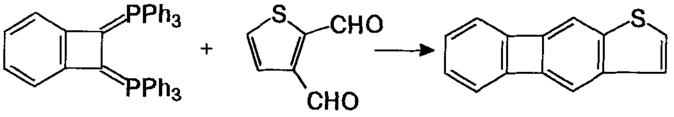
Ivergneux and coworkers systematically studied the dependence of the cyclization of ω-aldehydoylides on the number of atoms in the chain and found that the reaction proceeds with the formation of unsaturated lactones or dilactones[350]. Different heterocyclic compounds were obtained by means of Wittig bis-reactions. Five-membered rings were synthesized by Wittig reaction of α-diketones with bis-ylides, the ylide carbon atoms of which were separated by oxygen, sulfur, or by methylene groups (Eq. 6.153)[351–354]:



(6.153)

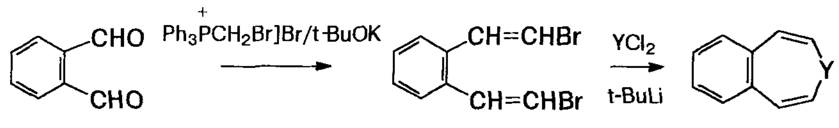
X=O (a), S (b), CH_2 (c)

Six-membered cyclic structures were synthesized by converting cyclobutene-1,2-bis-triphenylphosphonium bromide into bis-ylides, by the action of bases, and introducing the ylides into reaction with dialdehydes (Eq. 6.154)[355]:



(6.154)

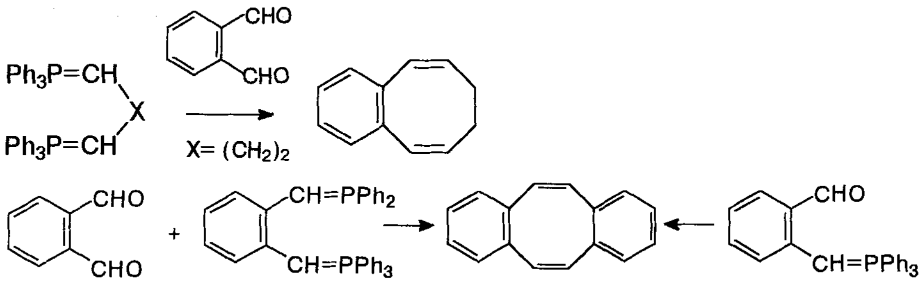
Versatile syntheses of benzoheteroepines have been developed (Eq. 6.155):



(6.155)

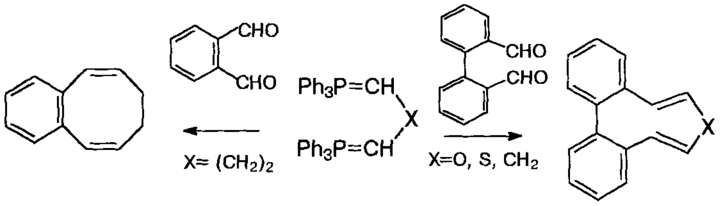
Y=AsPh, SbPh

The bis-Wittig reaction has been used to produce rings containing from eight to twenty-one-members; some examples have been reviewed.[273] Thus, benzocyclooctatetraene rings were obtained by use of the bis-Wittig reaction between phthalic aldehyde and a bis-ylide (Scheme 6.39):

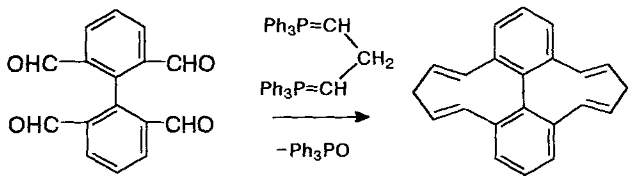


Scheme 6.39

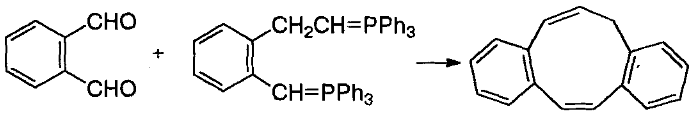
The reaction of phthalic aldehyde with *o*-bis(triphenylphosphonium methylide)benzene leads to the formation of dibenzo-cyclotetraene. This compound was also obtained by dimerization of the ylide generated by reaction of lithium ethoxide with formylbenzyltriphenyl-phosphonium chloride (Scheme 6.39).[356] Nine-membered rings have been prepared by reaction of bis-ylides with biphenyl-2,2-dialdehyde (Eq. 6.156–158)[359–361]. In another synthesis two consecutive bis-Wittig reactions of biphenyl-2,2,6,6-tetraaldehyde with a bis-ylide led to the formation of compounds bearing two nonadiene rings (Eq. 6.157)[361]. Derivatives of cyclononadiene have been synthesized by reaction of phthalic aldehyde with an asymmetric bis-ylide (Eq. 6.158)[362].



(6.156)

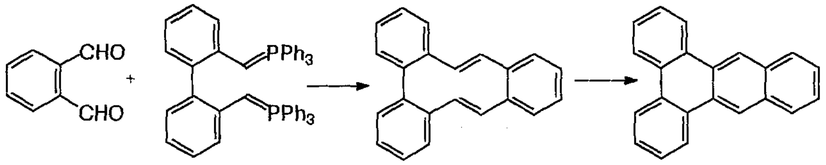


(6.157)

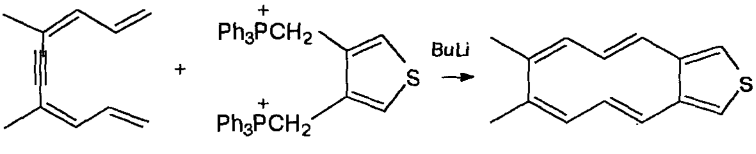


(6.158)

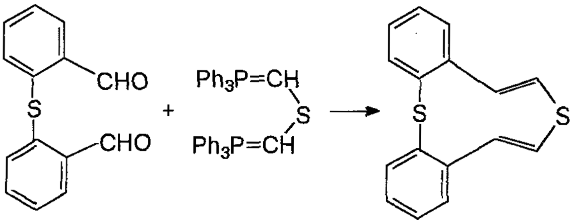
Several preparations of ten-membered rings by means of the bis-Wittig reaction have also been described (Eq. 6.159–161)[363]. Ten-membered cyclic dienes have been converted into derivatives of phenanthrene by electrocyclic transannular cyclization (Eq. 6.159)[364]. Stable [10]-annulenes have been obtained by reaction of bis-ylides with bis(2-formylhexenyl)sulfide (Eq. 6.160)[365]. 4-Bromo-1,6-methano-[10]-annulene-3-carbo-xylate has been prepared by a three-step synthesis, including a Wittig reaction, from cycloheptatriene-1, 6-dicarboxaldehyde (Eq. 6.161)[367]:



(6.159)

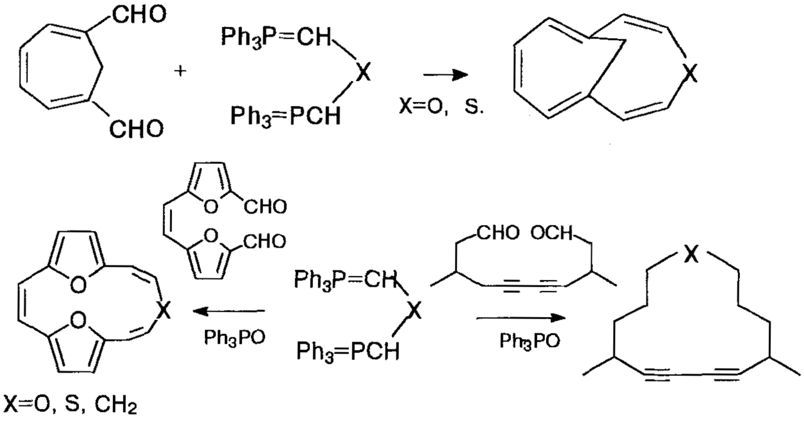


(6.160)



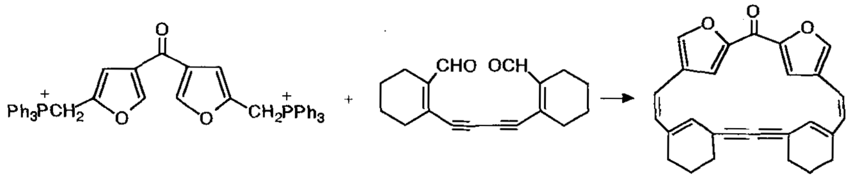
(6.161)

Syntheses of 11-, 12- and 13-membered annulenes by means of the bis-Wittig reaction are shown in Scheme 6.40[366–372]:



Scheme 6.40

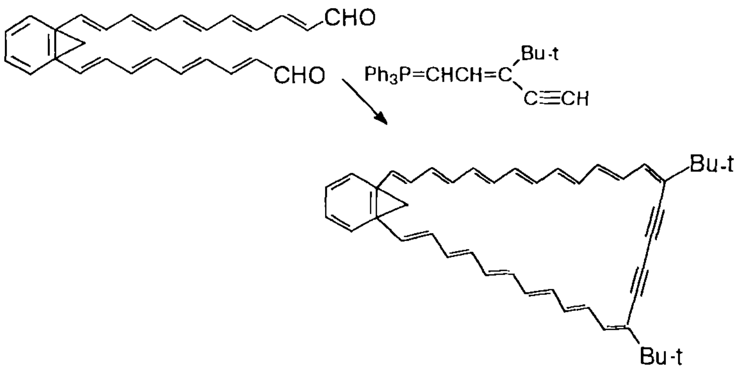
[19]- and [21]-Annulenes have been synthesized from phosphonium salts bearing furyl substituents and conjugated dialdehydes (Eq. 6.162)[373]:



(6.162)

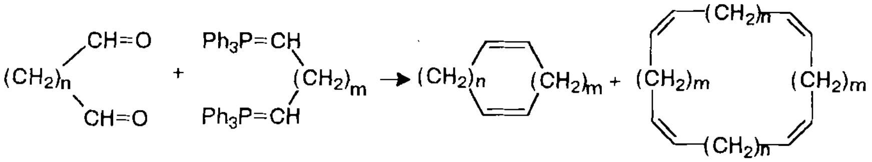
Higuchi and coworkers synthesized a 36-membered macrocycle, tetrahydro[36] annulene, by Wittig reaction of polyenedialdehyde with triphenylphosphonium (3-*tert*-butyl)pent-2-ene-4-ylide (Scheme 6.41)[357]:

The bis-Wittig reaction is usually accompanied by dimer formation (the tetra-Wittig reaction) resulting in a mixture of monomer and dimer (Eq. 6.163). The yield of the monomer increases when the bis-Wittig reaction leads to strained cyclic compounds. In these circumstances the tetra-Wittig reaction serves as a convenient method for the preparation of macrocycles:[374-381]

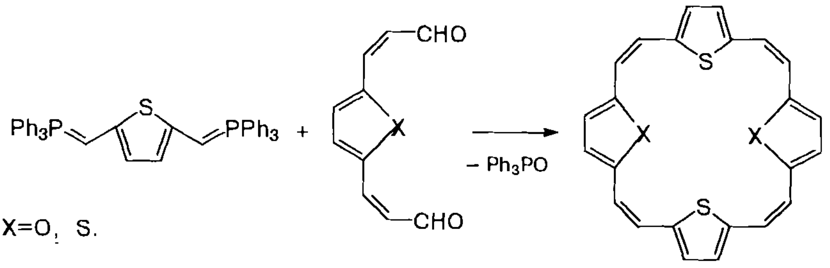


Scheme 6.41

Condensation of thiophene-2,5-bis(triphenylphosphoniummethylide) with thiophene 2,5-dicarboxaldehyde or with furan-2,5-dicarboxaldehyde affords [24]-annulenes (Eq. 6.164)[374]:

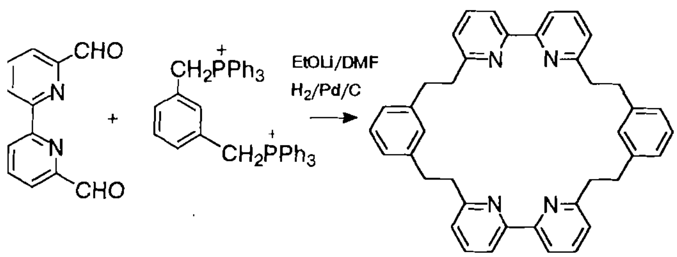


(6.163)

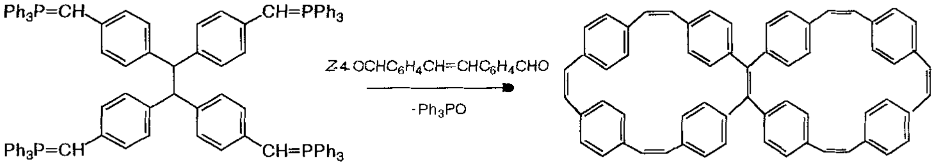


(6.164)

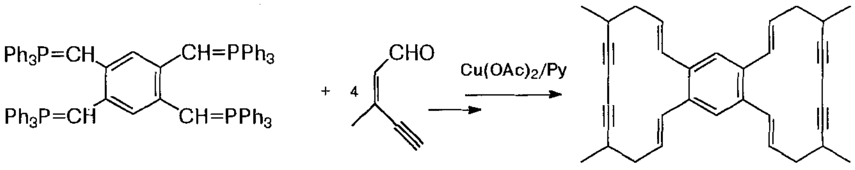
A 26-membered macrocycle bearing two bipyridyl structural units has been synthesized by use of a tetra-Wittig. reaction (Scheme 6.42)[375]:



Bicyclic cyclofan has been obtained by reaction of a tetrafunctional ylide with an unsaturated bis-aldehyde (Eq. 6.165)[376]. An interesting example has been described of the tetra-Wittig reaction of a tetraphosphonium salt with an enaminealdehyde resulting in the formation of a tetraacetylene. Cyclization of the tetraacetylene affords bis-[15]-annulene (Eq. 6.166)[377]:

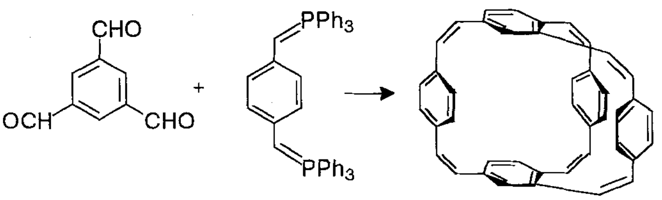


(6.165)



(6.166)

A variety of 18-, 20-, 24-, 26-, and 28-membered macrocyclic compounds have been prepared by the tetra-Wittig reaction[373,378,379]. Mathey and coworkers synthesized a fully unsaturated 24-membered tetraphosphorus macrocycle to study its coordination chemistry[381] and Thulin and Wennerstrom obtained a bis-cyclophan in the form of a cage (Eq. 6.167).[378]

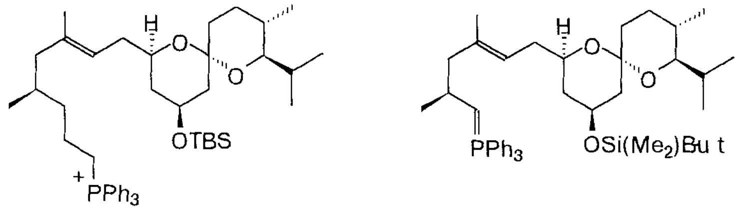


(6.167)

Macrolides

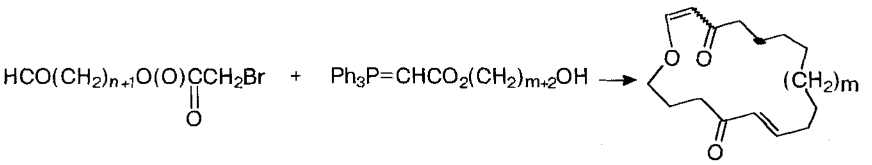
The important biological properties and interesting conformational features of the macrolide antibiotics have been the subject of many studies in recent years[382,383]. Elegant methodologies has been developed as a result of this impetus and applied to the total synthesis of macrolides.[384-391] Carbomycin B, and leucomycin A_3 methodologies have been developed on the basis of an approach that utilizes carbohydrate precursors and Wittig reaction[384,385].

The bis-, and tetra-Wittig reactions have been used for the synthesis of natural and biologically active macrocyclic compounds. A Wittig reaction of the ylide derived from a complex phosphonium salt has been used as the key step in a total synthesis of milbemycin (Scheme 6.43)[386]. An improved procedure, in which the ylide is generated in the presence of the aldehyde, has been used in the synthesis of several milbemycin derivatives[387], (+)-latrunculin A[388,390], macrocyclic diarylheptanoid garugamblin-2,[389b] plagiochins C and D[496], macrocyclic bis(bibenzyl)constituents of *Plaggiochila acantophylla*[389]:



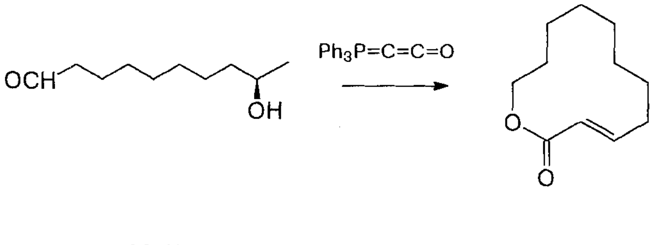
Scheme 6.43

The Wittig reaction with a suitably protected aldehyde has been used in studies directed towards the synthesis of the polyether macrolide halichondrin D (Eq. 6.168)[395]:

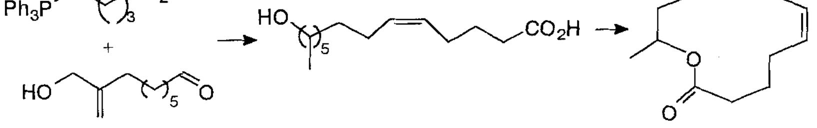


(6.168)

A new total synthesis of *R*-(+)-patulolide has been reported which uses triphenylphosphonium ketenylide in a coupling-cyclization sequence. The Wittig reaction in a key step involving P-ylides has been used extensively in the synthesis of six or seven macrolide components of pheromones of the grain beetles *Oryzaephilis* and *Cryptolestes* (Eq. 6.169)[391]. Floc'h and coworkers reported a method for the synthesis of macrocyclic components in which a short and convergent route to symmetrical and unsymmetrical unsaturated macrodiolides was realized by two consecutive Wittig reactions (Eq. 6.170)[392]:



(6.169)



(6.170)

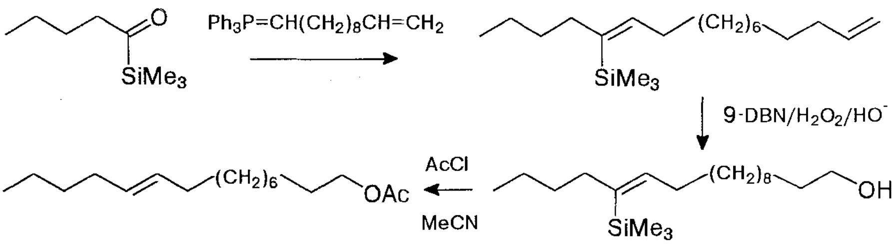
Examples of the application of the Wittig reaction in porphyrins syntheses have been described[393-396]. Iankov and coworkers reported the synthesis of porphyrin by Wittig reaction of formylporphyrin with a P-ylide[394] and Malinen and coworkers have prepared diisoprenyl-substituted porphyrins[396].

6.4.2 The Wittig Reaction in Natural Products Synthesis

Stereoselective Wittig reactions are widely used in the synthesis of natural products where, of course, the need to introduce double bonds in a controlled, stereospecific, or highly stereoselective manner is often of paramount importance. In this section we survey the use of this reaction in the field of natural product synthesis. Only relatively old reviews dedicated to the synthesis of naturally occurring compounds are accessible—those of Bergelson and Shemyakin (1954), Gosney and Rowley (1979), and Bestmann and Vostrowsky (1983). These reviews do not touch many important questions of modern natural products chemistry[397].

6.4.2.1 Synthesis of Pheromones

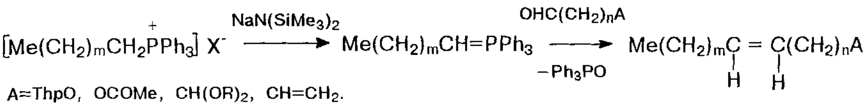
Pheromones are signaling substances by means of which insects exchange behavioral information. Very often insect pheromones are mono- or bis-olefinic aldehydes, alcohols and acetates, which can be easily obtained by use of the Wittig reaction.[397,421] A considerable contribution to the development of this method for the synthesis of pheromones was made by the Bestmann group[397]. The Wittig reaction has evident advantages over other methods in the preparation of pheromones: exact positioning of the C=C bond, the possibility of flexibly changing the *cis* or *trans* configurations of alkenes, and the stereochemical purity of the compounds formed[397-399]. Recent progress in the use of synthetic sex pheromones has emphasized the need for stereochemically pure alkenes for maximum effect. It is well known that even insignificant amounts of a second geometric isomer can completely change the action of the pheromone on an insect[401].For example, the reaction of acylsilane with phosphorus ylides in the presence of lithium salts affords the *Z*-vinylsilane in very high *E* stereoselectivity (>99%) (Scheme 6.44).[44]



Scheme 6.44

After removal of the trimethylsilyl group by treatment of the vinylsilane with acetyl chloride in acetonitrile, the stereochemically pure 11-hexadecene-1-ol acetate, identified as a sexual attractant, was obtained in high yield.

Z-Monoolefine pheromones can be obtained by *Z*-stereoselective Wittig reaction from phosphonium salts and aldehydes; sodium bis(trimethylsilyl)amide is used to generate the ylide from the phosphonium salt (Eq. 6.171)[402,403]:



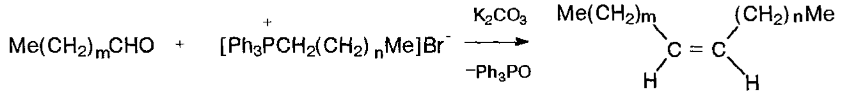
$$[\overset{+}{Me(CH_2)_mCH_2PPh_3}]\,X^- \xrightarrow{NaN(SiMe_3)_2} Me(CH_2)_mCH{=}PPh_3 \xrightarrow[-Ph_3PO]{OHC(CH_2)_nA} Me(CH_2)_m\underset{H}{C}=\underset{H}{C}(CH_2)_nA \qquad (6.171)$$

A=ThpO, OCOMe, CH(OR)$_2$, CH=CH$_2$.

Romanuk and coworkers used $H_2N(CH_2)_3NHLi$ in THF as a base in the Wittig reaction with aldehydes and obtained pheromones in 96–100% stereochemical purity[404].

Buschmann proposed a preparative method for the synthesis of *E,Z*-8-tetradecenyl acetate (e.g. *Z*:*E* = 9:1), pheromone of *Lepidoptera esp. spilonota ocellana.*The Wittig reaction of (8-hydroxyoctyl)triphenylphosphonium bromide with *n*-hexanal in the presence of sodium methylate furnished *E,Z*-8-tetradecene-1-ol and subsequent esterification with acetic anhydride resulted in the pheromone[405].

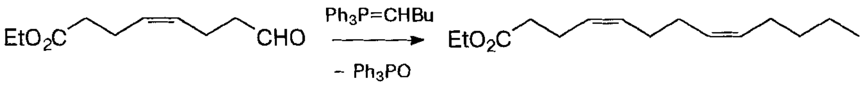
Le Bigot and coworkers[232] developed a *Z*-stereoselective method for the synthesis of pheromones by condensation of aliphatic aldehydes with phosphonium salts containing a long acyclic hydrocarbon chain, in aprotic solvents, in the presence of solid potassium carbonate as proton acceptor. Under these preparative conditions pheromones *Diptera musca domestica* and *Diptera musca autumnallis* were prepared in high yields and good *Z* stereoselectivity (Eq. 6.172):



(6.172)

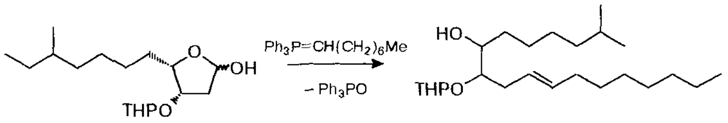
m=7-12, n=10-14

Andersen and Henrick described a method for the preparation of the sex-pheromone of the pink bollworm moth (*Gossyplur*). Careful investigation of the reaction conditions and the stereochemistry of the reaction between aldehyde and non-stabilized ylide enabled them to obtain the pheromone as a 1:1 mixture of *Z* and *E* alkenes (Eq. 6.173)[170]:

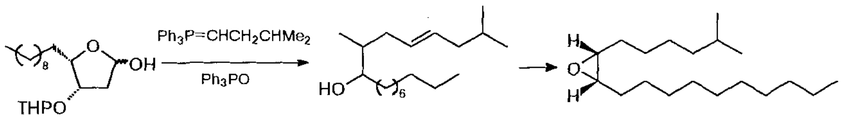


(6.173)

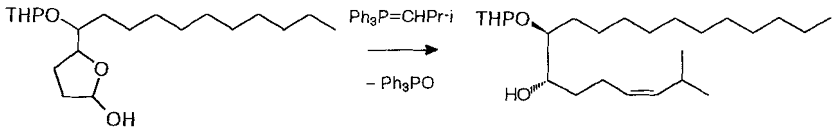
Lactols were used in the synthesis of optically active isomers of the sex-pheromone Disparlure produced by the female gypsy moth *Porthetria dispar L.* (Eq. 6.174). Both enantiomers of Disparlure were synthesized from 2*R*,3*R*-tartaric acid. The first enantiomer was obtained by reaction of the lactol with triphenylphosphonium isopentylide (Eq. 6.175)[407] and the second enantiomer by reaction of lactol with excess triphenylphosphonium isobutylide (Eq. 6.176)[408]:



(6.174)

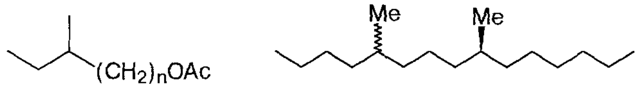


(6.175)



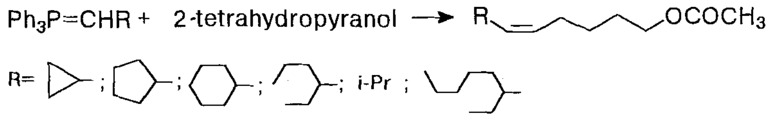
(6.176)

The chiral components of the pheromone adoxophyes were synthesized by means of the Wittig reaction and subsequent catalytic hydrogenation (Scheme 6.45, n = 9, 11)[409]. Standard Wittig methodology was used in the synthesis of the main components of the pheromones of *Leucotera scitella* and *Perileucotera coffeella*[410]:



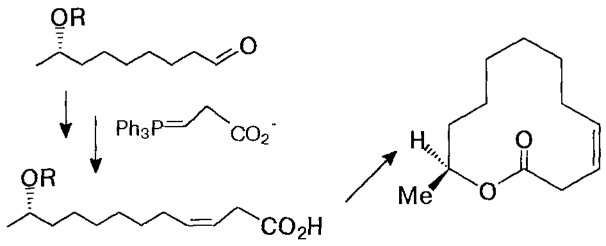
Scheme 6.45 n=9,11

Alkyl-branched and cyclic analogs of Z-5-decenyl acetate, the sex pheromone of the turnip moth, *Agrotis segetum*, have been synthesized using a Z-selective Wittig reaction (Scheme 6.46)[415]:



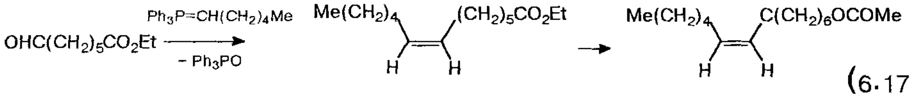
Scheme 6.46

Enantiospecific synthesis of S-(+)-methyleneicosan-2-one, an analog of the sex pheromone of the German cockroach (*Blatela germanica* L.), based on selective Bayer–Villiger and Wittig reactions, has been reported[411]. A simple method for the synthesis of (S)-3Z-dodecen-11-olide, the aggregation pheromone component of the rusty grain beetle *Cryptolestes ferrugineus*, has been developed by Moiseenkov and coworkers using Wittig reactions of chiral C_9-aldehyde, prepared from S-propylene oxide and C_3-P-ylide generated from 2-carboethoxytriphenylphosphonium bromide[42]. Boden and coworkers reported a similar method for the synthesis of macrocyclic components of the pheromones of the grain beetles of *Oryzaephilis* and *Cryptolestes ferrugineus* with the Wittig reaction in a key step (Scheme 6.47)[391]:

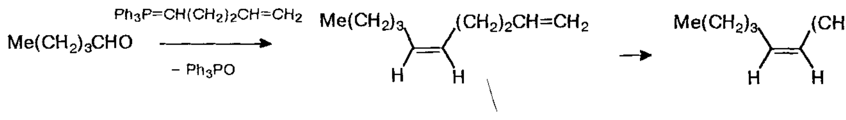


Scheme 6.47

Stereochemically pure 5-decenyl acetate, *Z*-7-dodecenyl acetate, *Z*-7-tetradecenyl acetate, and the *Z* components of pheromone of male turnip moth, were obtained by Wittig reaction of salt-free phosphorus ylides with the corresponding aldehydes (Eq. 6.177,178). Sodium bis(trimethylsilyl)amide was used to generate the ylides[403,412]:

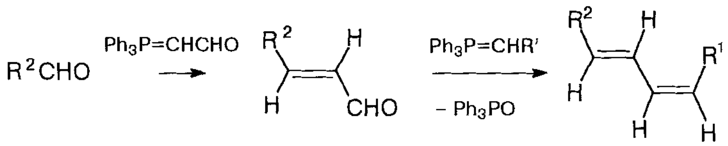


(6.177)



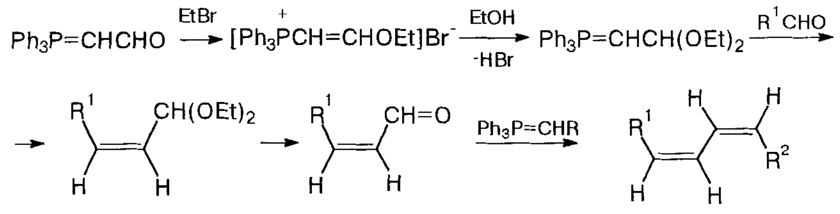
(6.178)

Highly stereoselective methods based on Wittig reactions for the synthesis of *Lepidoptera* pheromones were proposed by Bestmann and coworkers. Thus, reaction of an aldehyde with a stabilized ylide leads to the formation of *E*-α,β-unsaturated aldehyde with high *E* stereoselectivity. Subsequent Wittig reaction of this aldehyde with ylides under conditions ensuring high *Z* selectivity (for instance, reaction with non-stabilized ylides in aprotic solvents), affords *E*,*Z*-conjugated olefins (Eq. 6.179)[413,414]:



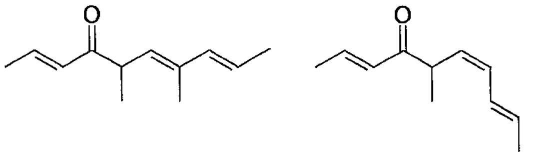
(6.179)

Another approach was developed for the preparation of α,β,Z,Z-conjugated olefins. Alkylation of the triphenylphosphonium α-formylmethylide with ethyl bromide furnishes the ethoxyvinylphosphonium salt, dehydrobromination of which and addition of ethyl alcohol to the ethoxyvinylylide formed affords the non-stabilized ylide. Wittig reaction of this ylide with an aldehyde affords an unsaturated acetal and then an unsaturated aldehyde which under the conditions of *Z*-selective Wittig reaction leads to the formation of α,β-*Z*,*Z*-conjugated diene. (Eq. 6.180). This compound has also been prepared by Wittig reaction of monoacetalglyoxal with a phosphorus ylide[416,417]:

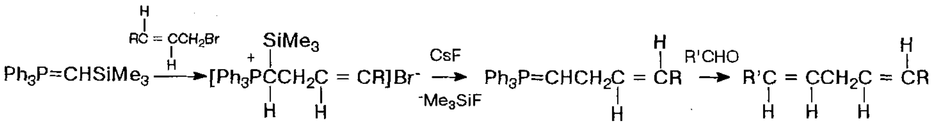


(6.180)

Syntheses of conjugated polyolefin sex-pheromones of Israeli pine blast scale were described by Israeli chemists:[418]:

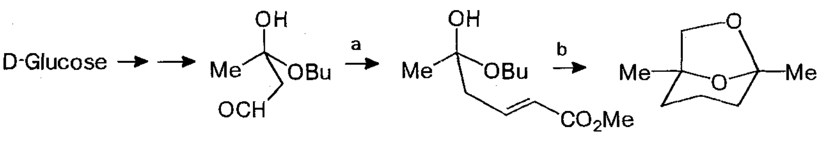


Polyolefins with multiple bonds separated by methylene groups are very important in the synthesis of the *Lepidoptera* pheromones. One approach to the synthesis of such polyolefins is based on the reaction of C-silyl-substituted ylides with cesium fluoride in the presence of carbonyl compounds. Reaction with the fluoride anion causes desilylation with splitting off of trimethylfluorosilane. This generates substituted ylides which at the moment of formation undergo the Wittig reaction with aldehyde to affords *E,Z*-1,4-dienes (Eq. 6.181)[397]



$$Ph_3P{=}CHSiMe_3 \xrightarrow{R\overset{H}{C}=\underset{H}{C}CH_2Br} [Ph_3\overset{+}{P}\underset{H}{\overset{SiMe_3}{C}}CH_2\underset{H}{C}=CR]Br^- \xrightarrow[-Me_3SiF]{CsF} Ph_3P{=}CHCH_2\underset{H}{C}=\overset{H}{C}R \xrightarrow{R'CHO} R'\underset{H}{C}=\underset{H}{C}CH_2\underset{H}{C}=\overset{H}{C}R \qquad (6.181)$$

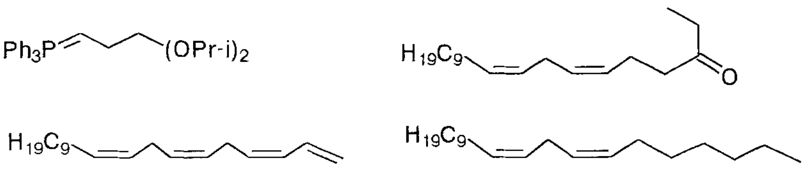
Jarosz and coworkers developed a synthesis of (–)-frontalin, the bark beetle pheromone, starting from D-glucose and using the Wittig reaction in a key step. The strategy of this synthesis uses the creation of the tertiary alcohol corresponding to C-1 in the target by using a carbohydrate template (Eq. 6. 6.182)[398]



(6.182)

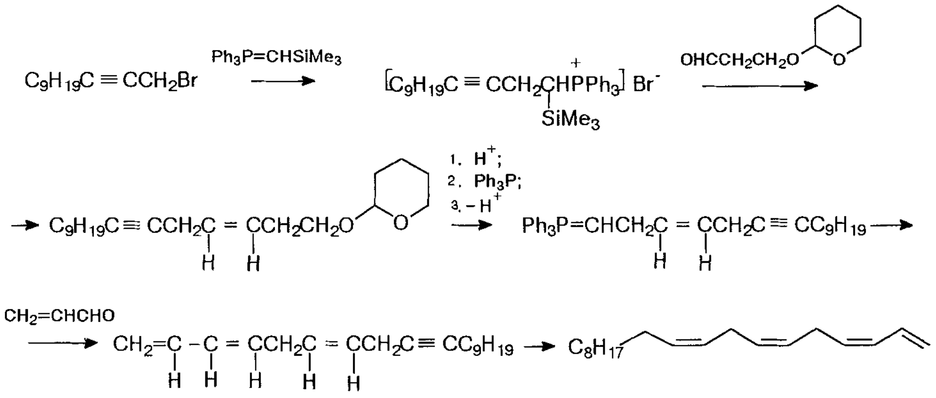
a=Ph3P=CHCOOMe/THF/refluxe; b= Pd/C, H2, EtOH

A synthesis of (+)-exo-brevicomin, a sex pheromone similar to frontalin, has been described by Streck and Fraser-Reid[406]. The syntheses of sex pheromones of the Winter moth *Operophtera brumata* involves the Wittig reaction of an ylide which acts as a homologating agent and enables further Wittig reaction after acetal deprotection (Scheme 6.48)[399]:



Scheme 6.48

Other syntheses of sex pheromones of *Operophtera brumata* is shown in the Scheme 6.49. Alkylation of triphenylphosphonium trimethylsilylmethylide with propargyl bromide affords a silicium-containing phosphonium salt. Desilylation of the salt in the presence of the aldehyde results in the formation of an enyne with a terminal protected hydroxyl group, which was first converted into an ylide and then by reaction with acrolein into a dieneyne. Reduction of the dieneyne with P-2 Nikel catalyst affords a tetraene, a component of the pheromone complex of *Operophtera brumata.*[419]

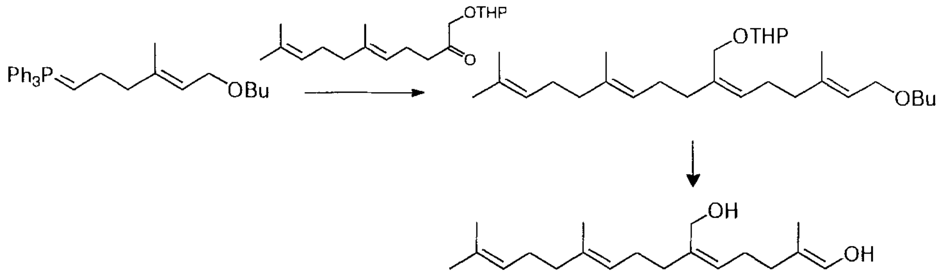


Scheme 6.49

cis Stereoselective Wittig reactions have been applied with great success to the synthesis of the pheromones of many *Lepidoptera*. Bestmann's group and other research groups applied these approaches for the syntheses of various pheromones. The results of these studies have been described in general articles[397,414]. The Wittig reaction has also been used in the synthesis of a variety of deuterium-labeled *Lepidoptera* pheromones and analogs [421]

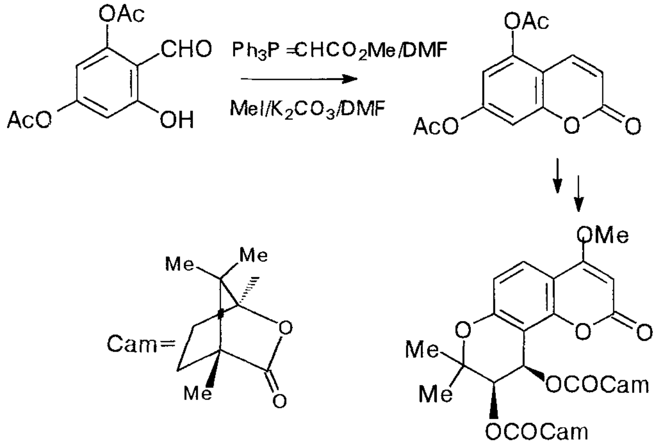
6.4.2.2 Syntheses of Pharmacology Products—Leukotrienes and Prostaglandins

The Wittig reaction is widely used in the synthesis of pharmaceuticals.[422-440] Examples of such syntheses are numerous. For instance, use of the Wittig reaction in a key step (Scheme 6.50) enabled the total syntheses of plaunotol, the main component of plaunoy, a remarkable drug from Thailand with high anti-ulcer activity[422]. Excellent *Z* stereoselectivity was achieved by Takayanagi and the resulting procedure applied to a stereoselective synthesis of plaunotol[423]:

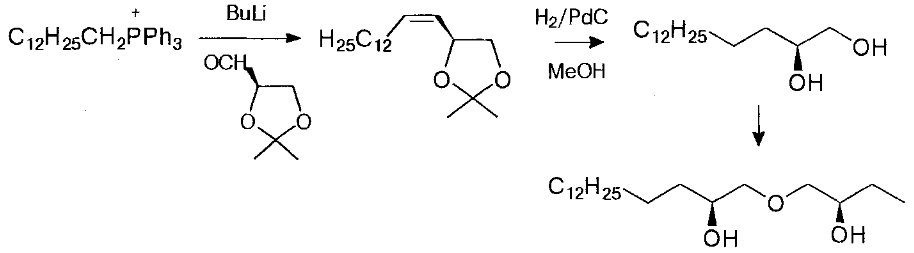


Scheme 6.50

The synthesis of methoxysubstituted Seselin analogs with extremely potent anti-AIDS activity against HIV-1 replication has recently been described by Takeuchi and coworkers (Scheme 6.51)[433]:



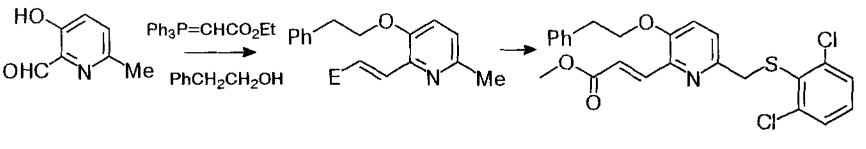
Scheme 6.51



Scheme 6.52

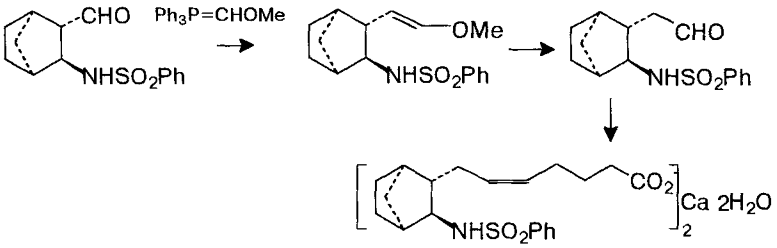
An efficient stereoselective synthesis of 2*S*,2′*S*-1-(2′-hydroxyhexadecyl)glycerol and its oxo analogs, potential antitumor compounds isolated from shark-liver oil, is shown in Scheme 6.52[425]:

The synthesis of *E*-3-[6-[[(2,6-dichlorophenyl)thio]methyl]-3-(2-phenylethoxy)-2-pyridinyl]-2-propenoic acid, a high-affinity leukotriene B_4 receptor antagonist with oral anti-inflammatory activity, was developed by Daines and coworkers by means of the Wittig reaction in the key step (Eq. 6.183)[426]:



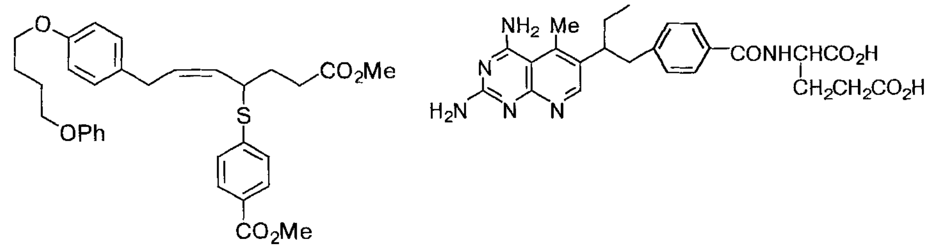
(6.183)

Methods based on the Wittig reaction are widely used in pharmaceutical compound synthesis. Examples include that of the thromboxane receptor antagonists S-1452,[430] its calcium salt[431] and combretastatin A4 analogs[427b]. The latter is orally active; various analogs are used as $F_2\alpha$ photoaffinity probes (Scheme 6.53)[432]:



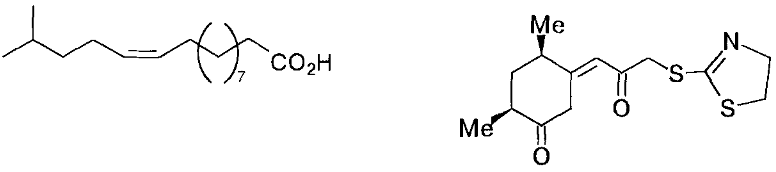
Scheme 6.53

The use of the Wittig reaction for the preparation of 4-[[4-alkoxycarbonyl) phenyl)thio]-7-[4-phenoxybutoxy)phenyl]-5-heptenoates, pharmaceuticals for the treatment of allergic disorders and inflammation, was patented by Meier and coworkers. These compounds are also leukotriene antagonists[428]. Synthesis of potential antifolates, 10-ethyl-5-methyl-5,10-dideazaaminopterin via the Wittig reaction of tributylphosphonium ylide, was described by Piper and coworkers (Scheme 6.54)[429]:



Scheme 6.54

A short synthesis of Z-15-methylhexadec-11-enoic acid, a component of*Cyanopsis tetragonolobus* and *Myxococacus xanthus* with marginal cytotoxicity against human cervix carcinoma (HeLa) and Chinese hamster ovary (CHO) cells, by use of the Wittig reaction was described by Reyes and, Carballeira[424]. Thiazoline analogs of apiderstatin, new inhibitor of the cell cycle of the FT-210 cells, were prepared in a racemic form by use of the Wittig reaction (Scheme 6.55)[434]:



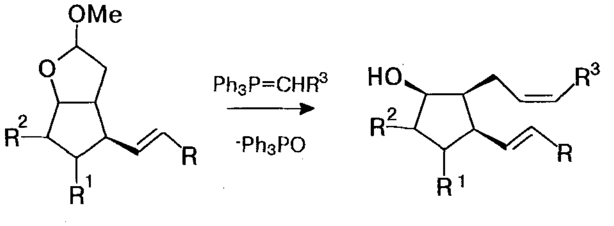
Scheme 6.55

The synthesis of virantmycin and (+)-Aphidicolin using the Wittig reaction in key steps was recently described by Japanese chemists.[435,436] Preparation of pyrrolidone derivatives, antithrombotic agents, by the Wittig reaction has been patented[427]. The synthesis of 5-styrylpyrimidines active against sigma-dopamine D and D_2 receptor binding sites was achieved by use of a stereoselective Wittig reaction[437]. Isochromophilone analogs, active against SP 120-CD_4 binding,[437a] and O,N-protected tunicamine[437b] were synthesised from sclerotiorin by Wittig reaction and aldol condensation.[437c]

The Wittig reaction is important synthetic tool in the synthesis of prostaglandins[438-457] and leukotrienes[458-510], which are too unstable to be easily obtained from natural sources.

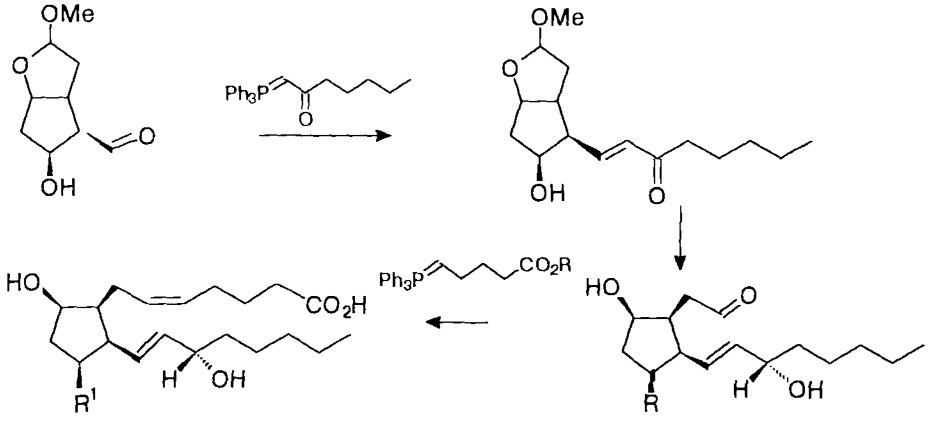
6.4.2.3 Prostaglandins

Prostaglandins are biologically active derivatives of unsaturated carboxylic acids containing more than 20 carbon atoms in the chain. The first methods for the synthesis of prostaglandins by use of Wittig reactions were developed by Corey (Eq. 6.187)[441].



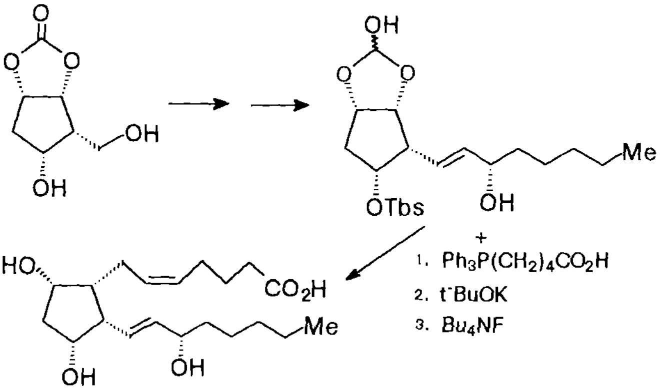
(6.184)

An industrial method for the synthesis of the PGF_2 using the Wittig reaction has been proposed. The prostaglandin was obtained in accordance with Corey's general scheme starting from lactol, which was subjected to two consecutive Wittig reactions with appropriate ylides (Scheme 6.56)[442]:



Scheme 6.56

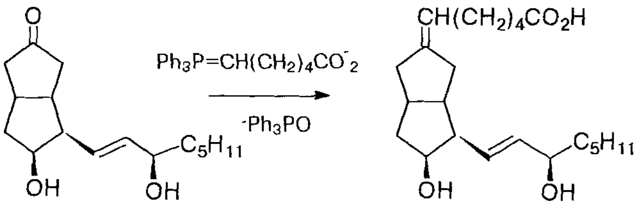
Another total synthesis of 12-*epi*-$PGF_{2}\alpha$ utilizes the radical cyclization of the *a*-glucose-derived thionecarbonate to give the key synthon [443]. Reaction with lactol of the ylide generated in DMSO enables construction of the *cis*-alkene lateral chains of racemic and optically active prostaglandins E_2 and F_2 (Scheme 6.57)[444]:



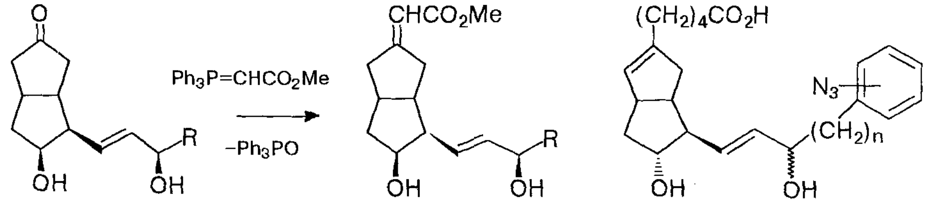
Scheme 6.57

Bioactive carbocyclic analogs of prostaglandin I_2, known as prostacyclin, were obtained analogously[445] Prostacyclin is a powerful inhibitor of platelet aggregation and a vasodilator in maintaining homeostatic circulation[446]. *E*/*Z* mixtures of 6-alkylbicyclo(3,3,0)octane-3-ylidene acetates containing mainly the *E* isomer were prepared by means of the Wittig reaction (Scheme 6.58)[458].

Suzuki and coworkers described the synthesis of prostacyclin analogs containing an azidophenyl group as a photoaffinity labeling functionality (Scheme 6.59)[448]:

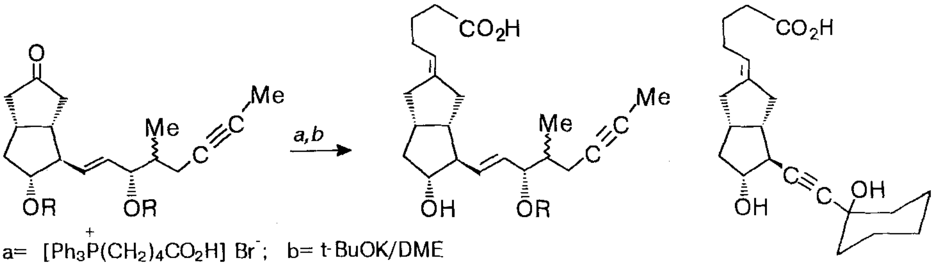


Scheme 6.58



Scheme 6.59

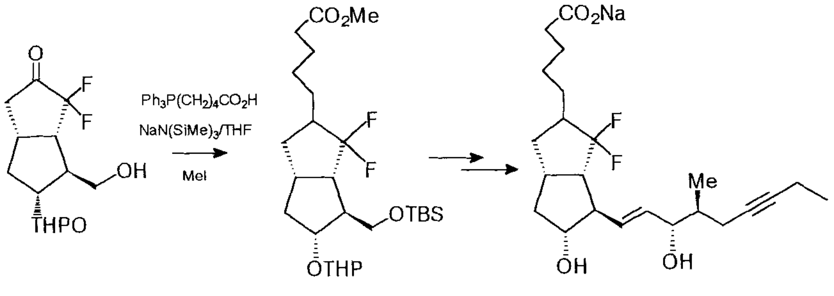
Use of the Wittig reaction with a salt to introduce the carboxylic acid side-chain in a synthesis of 15-non-stereogenic carbaprostacyclin led to a 1:1-mixture of the *Z*- and *E*-isomers[449]. The carbocyclin iloprost has been synthesized with 90% stereoselectivity by Wittig reaction of a bicyclic ketone with triphenylphosphonium 4-carboxybutylide (Scheme 6.60)[452]:



$a= [Ph_3\overset{+}{P}(CH_2)_4CO_2H]\ Br^-$; b= t-BuOK/DME

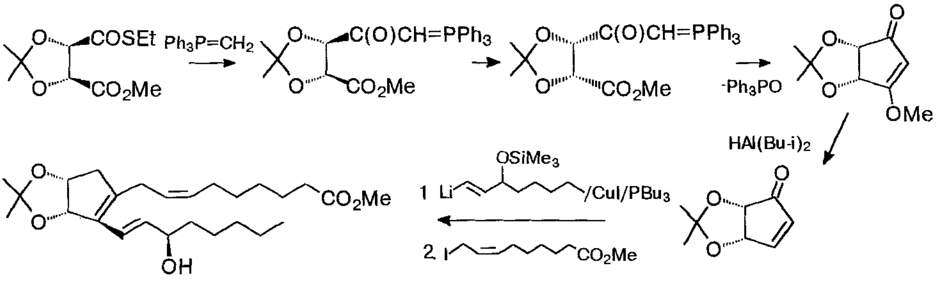
Scheme 6.60

Fluorine has unique physical properties derived mainly from its small atom size and high electronegativity. Introduction of fluorine into biologically active substances such as prostaglandins and thromboxanes is an important strategy in drug design[453]. Fluoroprostacyclin derivatives have been targeted as potentially stable drugs. The Wittig reaction of a difluorolactone with a phosphonium salt and with $NaN(SiMe_3)_2$ in THF proceeded smoothly to furnish a vinyl ether which was then converted into 7,7-difluoroprostacyclin with high inhibitor activity on ADP-induced human platelet aggregation in vitro (Eq. 6.185)[454]:



(6.185)

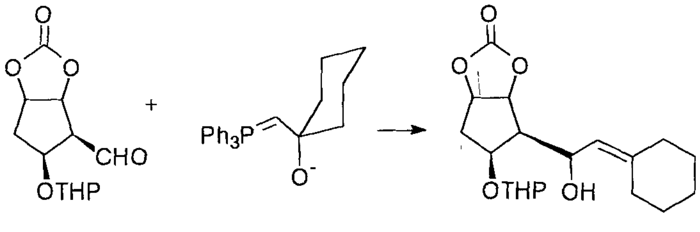
Optically active hydroxypentanones, the main fragments of prostaglandins, have been synthesized by Bestmann and coworkers[280] from *R,R*-tartaric acid thioester (Scheme 6.61).. The reaction of the thioester with triphenylphosphonium methylide furnished an acylated ylide. This was heated at high pressure (100 bar) to result in epimerization at the chiral center next to the ylide function with the formation of the 2*R*,3*S*-derivative, which underwent intramolecular Wittig reaction to give the acetonide of (4*R*,5*S*)-4,5-dihydroxy-3-methoxy-2-cyclopentenone. This cyclopentenone is a key compound in the enantioselective syntheses of a number of prostaglandins[455].



Scheme 6.61

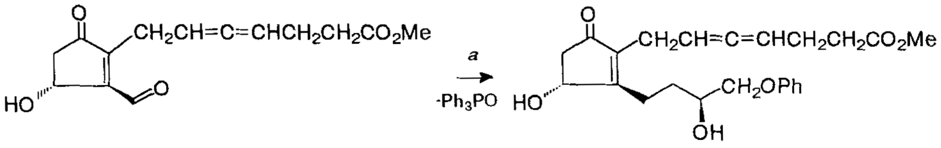
In the preparation of PGE$_2$ methyl ester (Scheme 6.61) the cyclopentenone was reduced to the alcohol with diisobutylaluminium hydride (Dibal). Allylic rearrangement of the alcohol afforded the *S,S*-acetonide of cyclopentenone, which underwent Michael addition to give the *S,S*-derivative. A tandem Michael addition was performed with the CuI–Bu$_3$P complex of the vinyllithium and then with the allylic iodide to produce PGE$_2$ methyl ester

Stereoselective syntheses of prostaglandins have been developed on the basis of *β*-oxide ylides (See Section 6.5.3) (Eq. 6.186).[450]



(6.186)

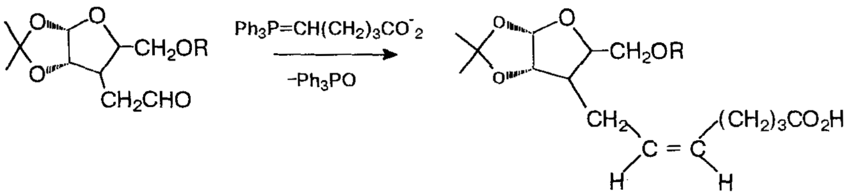
Analogs of prostaglandins have been obtained by Wittig reaction of cyclopentanecarboxaldehyde with a P-ylide in dioxane (Eq. 6.187)[451]:



a=Ph3P=CHCH(OH)CH2OPh

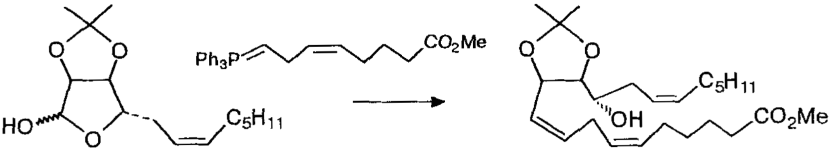
(6.187)

Methods have been developed for the synthesis of oxaprostaglandin derivatives starting from 2-ribofuranose. Wittig reaction of an aldehyde with the sodium salt of an ylide provided an acid which was used as an intermediate product in the synthesis of oxaprostaglandin (Eq. 6.188)[456]:



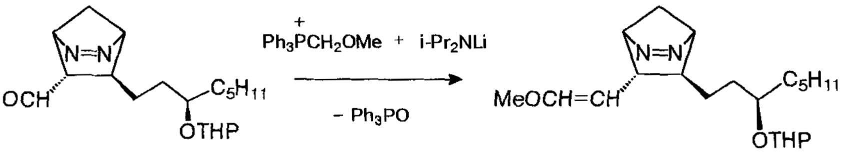
(6.188)

Wittig olefination of the lactol with a phosphorus ylide is also a key step in the synthesis of the methyl ester of 10*S*-hepoxilin B3 and 10*S*-trioxilin B3 (Eq. 6.189)[457]:



(6.189)

9,11-Azo-analogs of endoperoxide PGH$_2$ were synthesized by Wittig reaction of methoxymethylide, generated from a phosphonium salt and lithium diisopropylamide, with an aldehyde (Eq. 6.190)[447]:

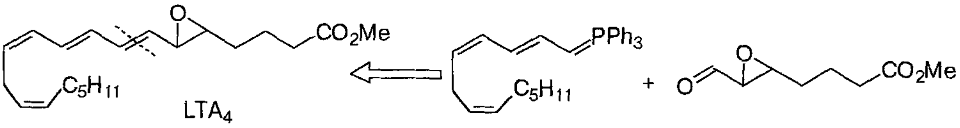


(6.190)

6.4.2.4 Leukotrienes and Related Compounds

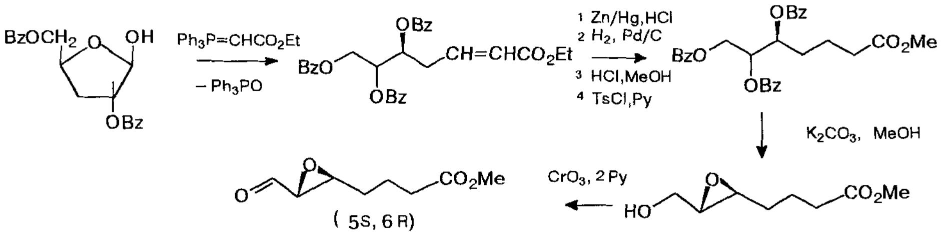
The term leukotrienes was first introduced by Samuelsson to describe a family of unsaturated C_{20} carboxylic acids biosynthesized from 5Z,8Z,11Z,14Z-eicosatetraenic acid (arachidonic acid)[459]. These compounds were first identified in leucocytes and the characteristic feature is a conjugated triene unit. Structurally different leukotrienes (LT) are distinguished by the letters A to E. Since LT can be produced from 5Z,8Z,11Z-, 5Z,8Z,11Z,14Z-, and 5Z,8Z,11Z,14Z,17Z-eicosenoic acids, a subscript is added to denote the number of double bonds in the molecule. The special feature of the leukotriene structure is the absence of a ring in the molecule. Depending on the structure of the functional groups on the carbon chain, leukotrienes are divided into types A, B, C, D, and E, and depending on the number of double bonds into series 3, 4, and 5. The natural prostaglandins, thromboxanes, and leukotrienes are formed from general precursors, polyunsaturated fatty acids containing appropriate number of carbon atoms and new bonds, i.e. linoleic and serakidon acids[439,440,460]. Since the discovery of the leukotrienes there has been an enormous ongoing effort to synthesize these products and analogs. A review describing the leukotrienes has been published by Green and Lamberth[438].

The preparation of (±)-LTA$_4$, an important mediator of anaphylaxis, was first described in 1979 by Corey who used the Wittig reaction for the synthesis of leukotrienes[460]. Corey proposed the strategy of total synthesis of the C_{20}-molecule of Wittig A$_4$ and developed syntheses of leukotriene building blocks (Scheme 6.62):



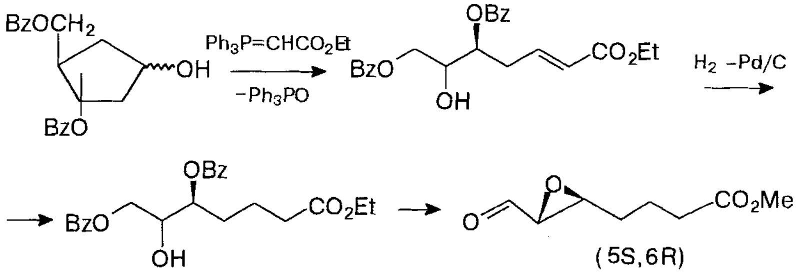
Scheme 6.62

Syntheses of optically active 5*S*,6*R*-epoxyaldehyde, C_7-building block for the preparation of LTA$_4$ was performed by Wittig reaction of the 2,3,5-tribenzoyl derivative of D-(–)-ribose starting from triphenylphosphonium ethoxycarbonylmethylide and furnished the olefin as a mixture of *Z* and *E* isomers. (Scheme 6.63)[460]:



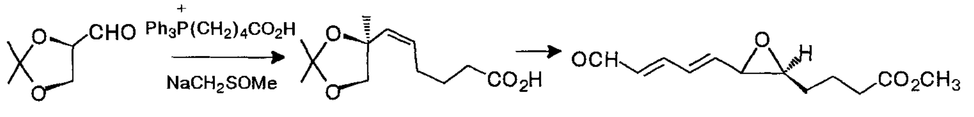
Scheme 6.63

Subsequent deoxygenation of the olefin, hydration, treatment with dry hydrogen chloride in methanol, and deprotection led to the 5*S*,6*R*-epoxyalcohol. Oxidation of the epoxyalcohol using excess Collins reagent afforded 5*S*,6*R*-epoxyaldehyde. Later Marriot and Bantick[167] used 2-desoxy-D-ribose as the starting compound in a considerably simplified method for the synthesis of C_7-5*S*,6*R* epoxyaldehyde (Scheme 6.64):



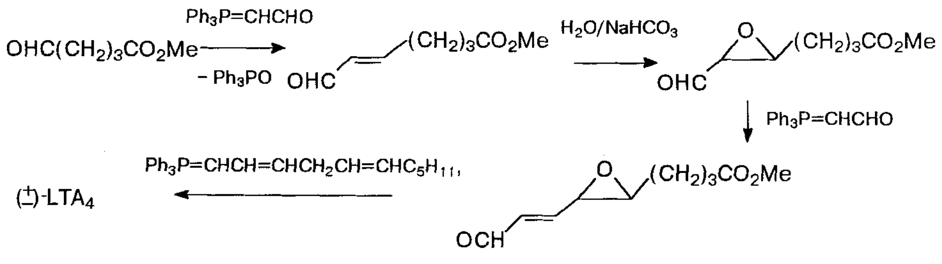
Scheme 6.64

Rokach[461] described a method for the preparation of 5*S*,6*R*-epoxyaldehyde from D-glyceraldehyde as a chiral synthon. The reaction of the 5*S*,6*R*-epoxyaldehyde with a ylide generated from a phosphonium salt with butyl lithium in toluene resulted in the methyl ester of racemic LTA_4 in a yield of 50% (Eq. 6.191)[463]:



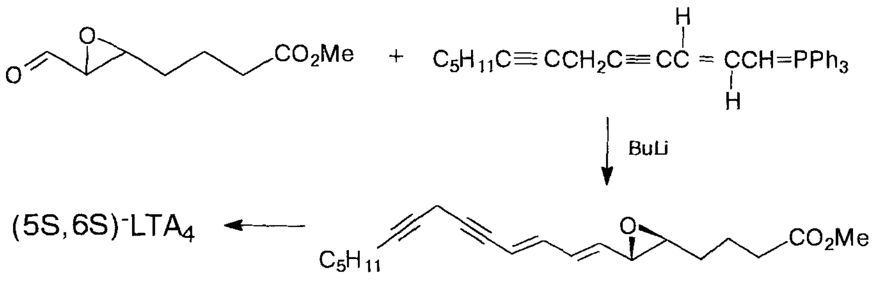
(6.191)

Gleason and coworkers[463] proposed a four-step method for the synthesis LTA_4 from methyl 4-formylbutyrate. The appropriate triphenylphosphonium undecadienylide was prepared from oct-2-yn-1-ol (Scheme 6.65):



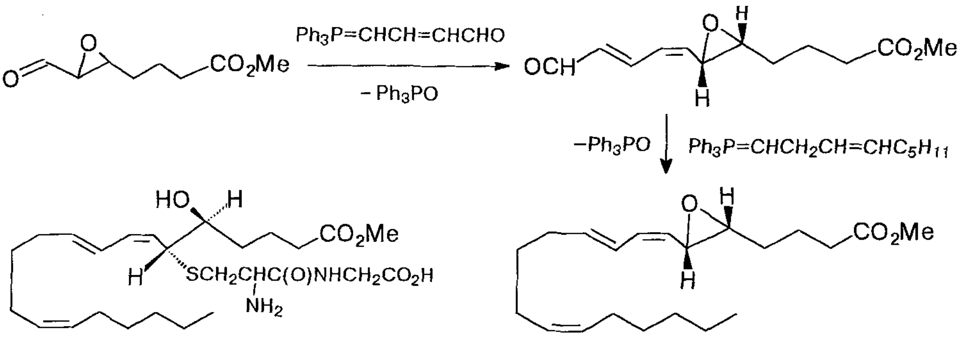
Scheme 6.65

Tolstikov and coworkers described the reaction of 5*S*,6*R*-epoxyaldehyde with an ylide generated from the appropriate phosphonium salt by butyllithium resulting in the mixture of bis-dehydroleukotriene A_4 methyl ester and its 7*Z* isomer in 21:79 ratio. The reduction of the bis-dehydroleukotriene A_4 methyl ester with Lindlar catalyst led to the formation of 5*S*,6*S*- LTA_4 methyl ester (Scheme 6.66).[465]:



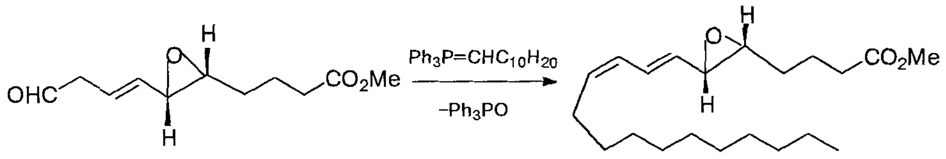
Scheme 6.66

Methods for the formation of the LTA_4 polyene chain were developed using the Wittig reaction of 5*S*,6*R*-epoxyaldehyde with 3-formylpropenylide, leading to the formation of C_{11}-epoxydienal. The Wittig reaction of the latter with C_9-allylide ($C_{11} + C_9 = C_{20}$) afforded LTA_4 (Scheme 6.67). LTD_4 was prepared analogously[470].



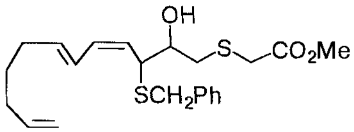
Scheme 6.67

The Wittig reaction was used for the synthesis of tetrahydro-7*E*,9*Z*-leukotriene A methyl ester (Eq. 6.192)[471]:

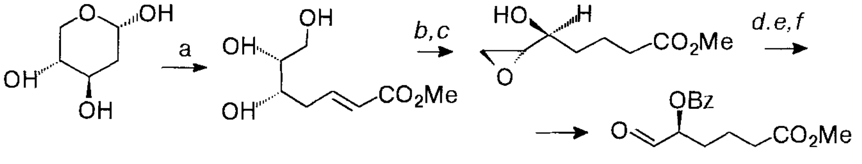


(6.192)

The reaction of 3-formylpropenylideneylide with aldehydes and subsequent isomerization of the resulting olefin under the catalytic action of iodine led to the formation of an aldehyde that was subsequently converted into thioleucatriene A_4 by the Wittig reaction[472]



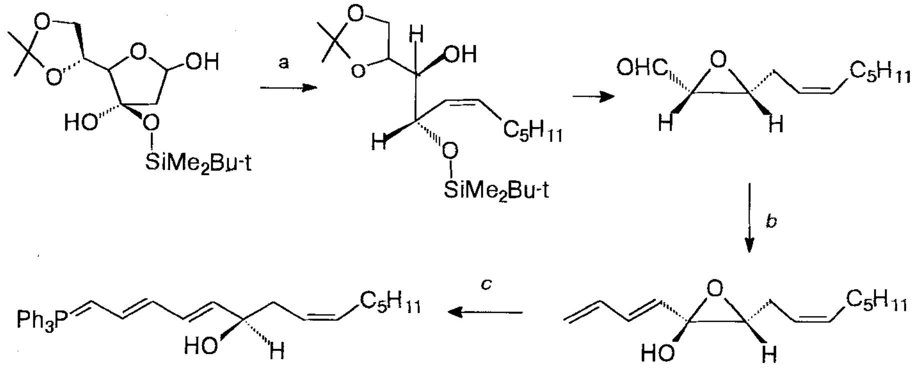
The Wittig reaction was also used to obtain leukotriene B_4, an important mediator of inflammation. The Wittig reaction between 2-deoxy-D-ribose and triphenylphosphonium methylide resulted in the formation of a hydroxyester. Subsequent tosylation, cleavage of the acetal and the reaction of the glycol with potassium carbonate in methanol afforded an epoxide which was converted into *S* aldehyde, a key (C_6) building block of LTB_4, as Eq.193 shows[473,474]:



(6.194)

a) $Ph_3P{=}CHCO_2Me$; *b*)$TsCl/Py$; *c*) $K_2CO_3,MeOH$; *d*) $TsCl/Py$; *e*) $HClO_4/(MeO)_2CO/H_2O$; *f*) $Pb(OAc)_4$

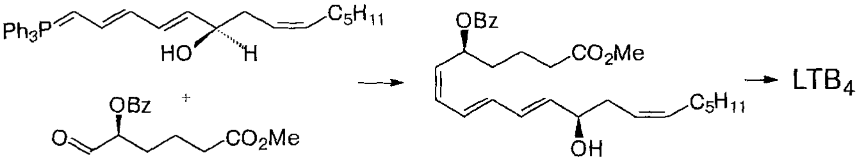
The second building block for the preparation of LTB_4, the C_{14} ylide, was obtained from an acetal-protected carbohydrate, which by the Wittig reaction was stereospecifically transformed into the *cis* olefin. The olefin was used to prepare the epoxyaldehyde and hence the epoxytriene. Addition of HBr to the epoxytriene and reaction of the bromide formed with Ph_3P afforded the appropriate phosphonium salt, treatment of which with butyllithium led to the C_{14} ylide (Scheme 6.68):



a) $Ph_3P{=}CHC_5H_{11}$; *b*) $Ph_3P{=}CHCH{=}CH_2$; *c*) $HBr/Ph_3P/BuLi$

Scheme 6.68

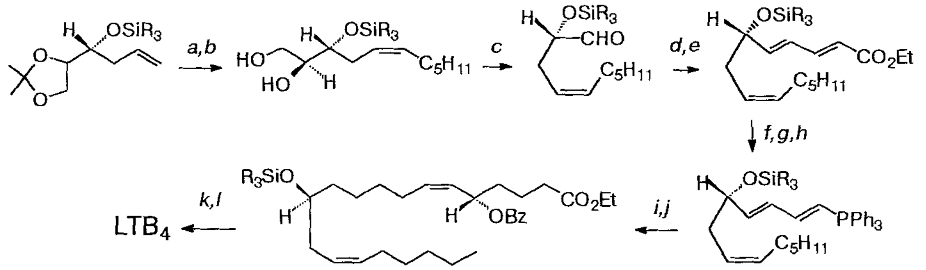
The C_{14} ylide was then reacted with the aldehyde in THF solution containing hexametapol, to furnish the benzoyl derivative of LTB_4, which after deprotection afforded free LTB_4 (Eq. 6.194)[473]:



(6.194)

A method for the synthesis of the C_{14}-allylide using the Wittig reaction of 2-desoxy-D-ribose with triphenylphosphonium carboethoxymethylide was described by Rokach and coworkers[475].

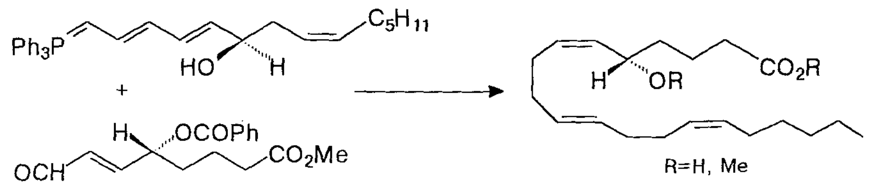
The total syntheses of (+)-LTB_4, has been realized on the basis of two enantiomerically pure *α*-hydroxyaldehydes, key chiral synthons. The first chiral aldehyde was prepared from arabinose. Wittig reaction of this aldehyde with triphenylphosphonium hexylide afforded the unsaturated chiral alcohol, which was oxidized to the aldehyde. This was then subjected to consecutive Wittig reaction with triphenylphosphonium formylmethylide and Horner–Wittig reaction with phosphonoacetic ester to result in the C_{14}-ester. The ester was reduced to the alcohol, converted to the bromide, and reacted with triphenylphosphine oxide with the formation of the C_{14}-phosphonium salt. Wittig reaction of this salt with 5*S*-aldehyde resulted in the leukotriene silyl ester which after deprotection and hydrolysis was converted into free LTB_4 (Scheme 6.69)[476,477]:



a=$Ph_3P{=}CHC_5H_{11}$; b=$CF_3CO_2H/THF/H_2O$; c=$Pb(OAc)_4$, Na_2CO_3; d=$Ph_3P{=}CHCHO$; e=$(EtO)_2P(O)CHCO_2Et$; f=AlH_3; g=PPh_3; h=CBr_4/PPh_3; i=BuLi; j=$MeO_2C(CH_2)_3C(OBz)CHO$; k=Bu_4NF; l=$K_2CO_3/MeOH$

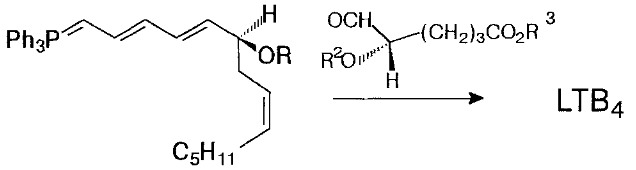
Scheme 6.69

Syntheses of LTB_4 by Wittig reaction of C_{14}-allylide and C_6-aldehyde has been described[478,479]:



Scheme 6.70

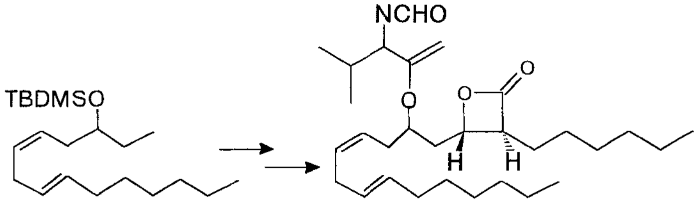
It should also be noted that a synthesis of LTB_4 from D-xylose uses the Wittig reaction in one of the key steps[480,481]. Eicosatetraenic acid (the geometric isomer of LTB_4) has also been synthesized via the use of the Wittig reaction in a key step (Scheme 6.70)[482]. A new convergent syntheses of LTB4 involves the Wittig reaction of the P-ylide with an aldehyde as a key step (Eq. 6.195)[483]:



(6.195)

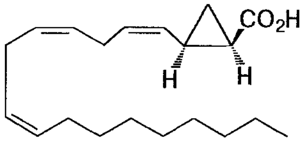
Arsenic ylides have been used in a Wittig reaction to introduce the C_6-Z-alkene function in a synthesis of 3-hydroxyleukotrienes B_4 (3-OH-LTB_4)[484].

The key intermediate of (–)-lipstatin, a potent inhibitor of pancreatic lipase, was obtained by two Z-stereoselective Wittig reactions[485]. Several positional isomers of leukotrienes and the corresponding intermediates have been prepared by use of a chemical procedure generally similar to those employed for the synthesis of the naturally occurring compounds (Scheme 6.71).

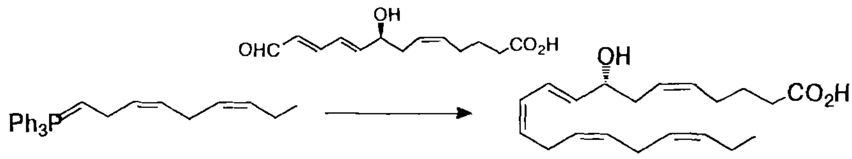


Scheme 6.71

A cyclopropyl analog of arachidonic acid has been prepared by use of a Z-selective Wittig reaction[486].

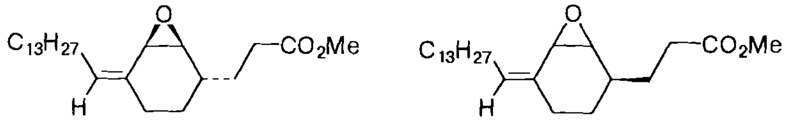


The first total synthesis of a barnacle hatching factor has been achieved by use of a Wittig reaction with a P-ylide (Eq. 6.196)[488] and the enantioselective total synthesis of an arachidonic acid metabolite 3-hydroxyeisosatetraenoic acid has been reported[487].



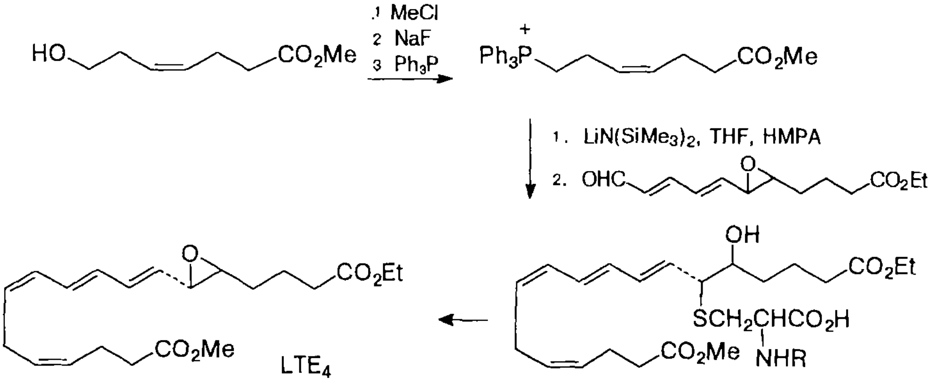
(6.196)

Conformationally-restricted LTD_4 analogs have been synthesized by use of stereoselective Wittig olefination as the key step (Scheme 6.72)[489]:



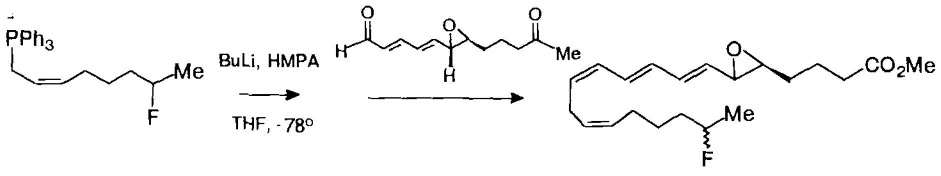
Scheme 6.72

Many syntheses of leukotrienes are exceedingly complex multi-step sequences of reactions. Application of the Wittig reaction in the key steps of these reaction schemes facilitates the preparation of leukotrienes. Thus, the synthesis of leukotrienes LTE_4 was realized as a result of the formation of a C_{11}–C_{12} *cis* double bond by Wittig reaction of the chiral diene epoxide aldehyde (Scheme 6.73)[491]:



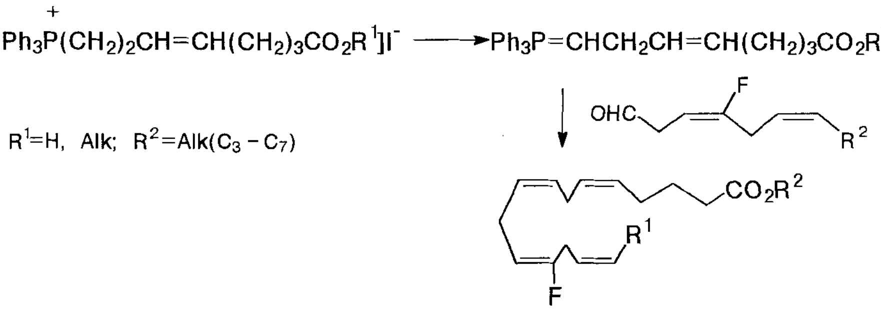
Scheme 6.73

Garsia and coworkers[492] and Kukhar and coworkers[493] have reported general syntheses of fluorine-containing derivatives of LTA_4 (Scheme 6.74):



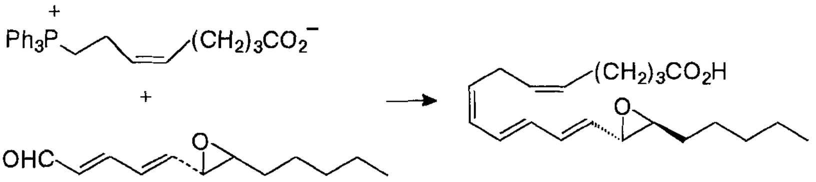
Scheme 6.74

Fluorine-containing analogs of leukotrienes, highly effective inhibitors of cyclooxahenase and 5-lipoxyhenase, were obtained by means of the Wittig reaction. A suspension of phosphonium salt in THF was treated with butyllithium and then with aldehyde. The mixture was stirred for 20 min at 20°C to give the 1,2-fluoroarachidonate (Scheme 6.75)[494]:



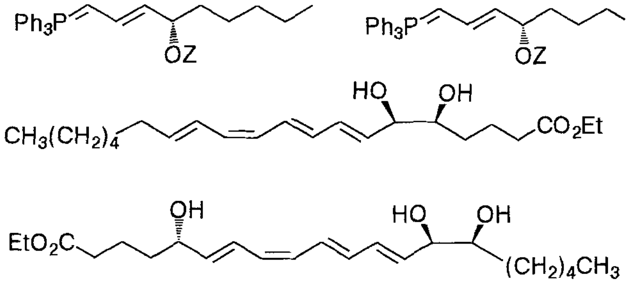
Scheme 6.75

Total stereospecific synthesis of oxido(5*Z*,8*Z*,10*E*,12*E*)-eicosatetraene acid was performed with the Wittig reaction as a key step (Scheme 6.76)[495]:



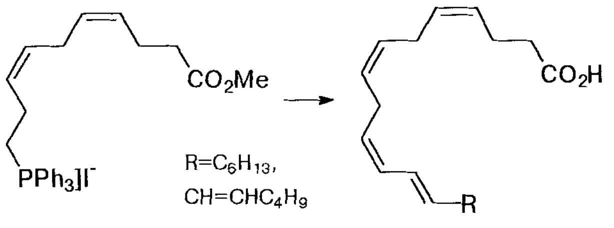
Scheme 6.76

Phosphonium and arsonium ylides were used in the synthesis of lipoxins A_4 and B_4 (LXA_4 and LXB_4), again with a Wittig reaction in a key step. LXA_4 and LXB_4 were obtained as a 1:1 mixture of the *Z* and *E* isomers which were separated by HPLC (Scheme 6.77)[496,497]:



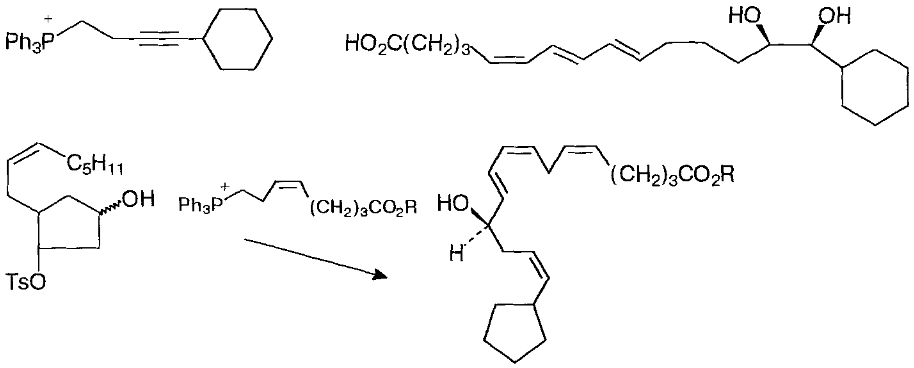
Scheme 6.77

A C_{10} phosphonium salt has been used as a starting building block in the synthesis of arachidonic acid analogs (Eq. 6.197)[498]:



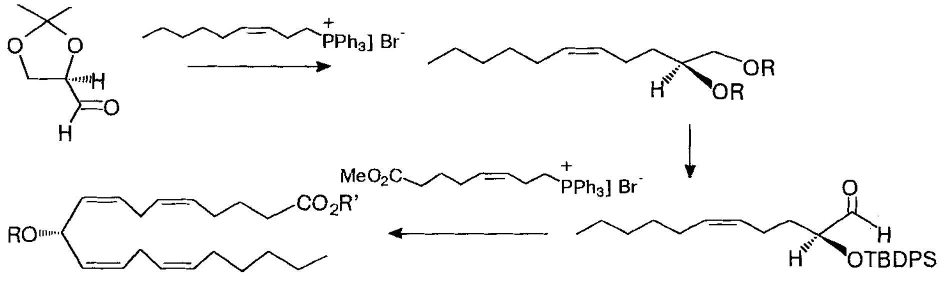
(6.197)

Other similar examples of the Wittig olefination in such syntheses include the use of an acetylenic ylide in a new total synthesis of 11*R*,12*S*-diHETE[499] by concise synthesis if fatty acids containing the *R*-hydroxy-*E*,*Z*-diene subunit[500]. Three equivalents of ylide were used to induce elimination of tosylate and subsequent Wittig condensation (Scheme 6.78)



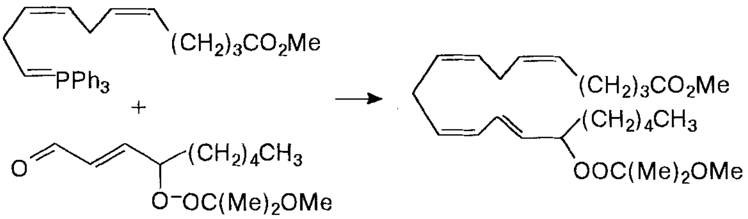
Scheme 6.78

Hydroxyeicosatetraenoic acids (HETEs) are formed in numerous types of cell by enzymatically-mediated hydroxylation of arachidonic acid. 10*S*-(–)-hydroxyeicosa-5*Z*,8*Z*,11*Z*,14*Z*-tetraenoic acid methyl ester was synthesized starting from enantiomerically pure R-glyceraldehyde acetonide (Scheme 6.79)[501]:



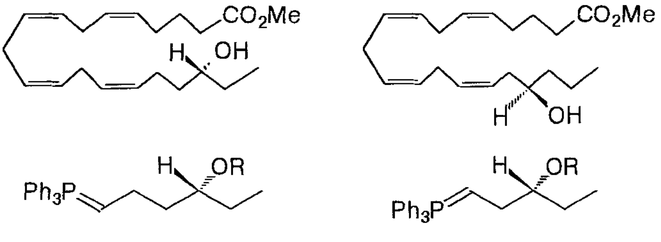
Scheme 6.79

One synthesis of a 15*S*-HETE uses the Wittig reaction of a P-ylide to construct the eicosane skeleton (Scheme 6.80)[502]:

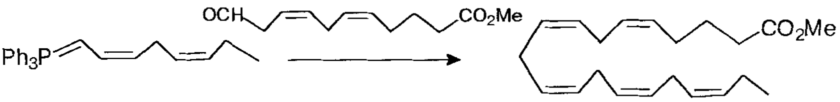


Scheme 6.80

The Wittig Reaction is the method of choice for the synthesis of eicosatetraenoic acids and their derivatives. These methods include the preparation of 17-*R*- and 18-*R*-hydroxyeicosatetraenic acids from chiral P-ylides (Scheme 6.81)[503] and the preparation of all-*cis*-5,8,11,14,17-eicosapentaenoic acid from nona-3,6-dienyltriphenylphosphorane and an unsaturated aldehyde (Eq. 6.198)[504]:

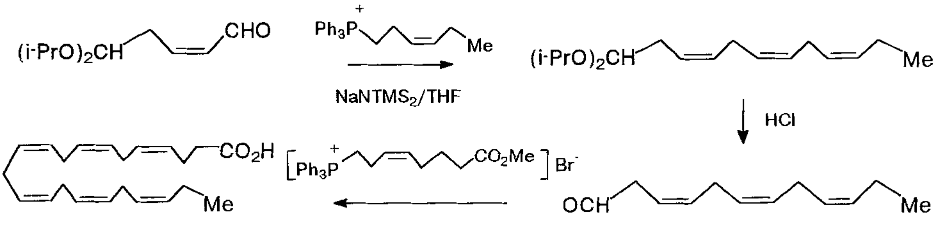


Scheme 6.81



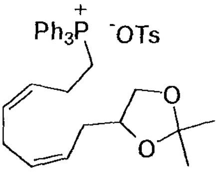
(6.198)

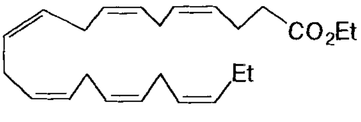
Sandri and Viala reported the synthesis of all-*Z*-5,8,11,14,17-eicosapentanoic acid and all *Z*-4,7,10,13,16,19-docosahexaenoic acid from *Z*-1,1,6,6-tetraisopropoxy-2-hexene. These compounds were used either as ylides or as carbonyl compounds in subsequent Wittig reactions leading stereoselectively to the eicosapentanoic acid (Scheme 6.82)[505]:



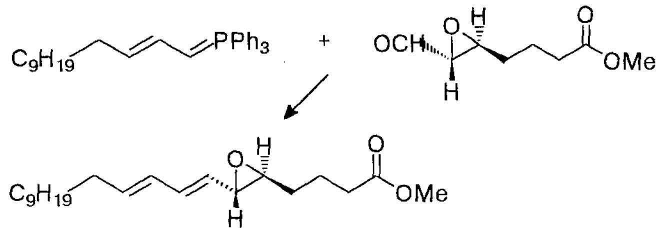
Scheme 6.82

The preparation and subsequent Wittig reaction of a *Z*,*Z*-phosphonium salt as a useful novel synthon for the preparation of skipped conjugation polyenes has been reported.[506] This synthon was used as a key intermediate in the synthesis of ethyl all-*Z*-4,7,10,13,16,19-docosahexaenoate[342].



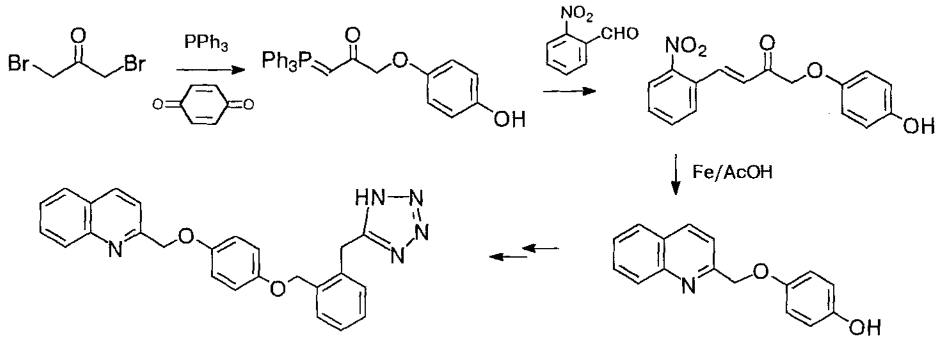


Rokach and coworkers reported the synthesis of 12-ketoeicosatetraenoic acid (12-KETE) and its 8,9-*trans* isomer based on the Wittig reaction[508]. A key step in a reported synthesis of novel photoactivatable 7*Z*,9*E*- and 7*E*,9*E*-dienic peptidoleukotriene derivatives is a Wittig reaction between the *E* phosphonium ylide and the chiral epoxy aldehyde resulting in a 3:1 mixture of the 7*Z*,9*E*- and 7*E*,9*E*-dienes (Scheme 6.83)[509]:



Scheme 6.83

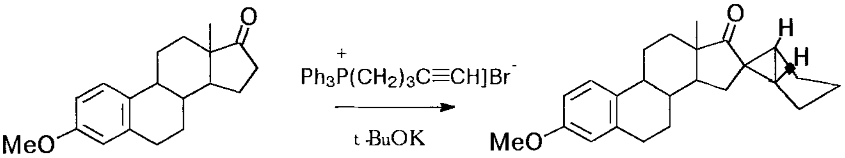
O'Brien and coworkers proposed new synthetic approaches to RG 12525, a commercially interesting antagonist of LTD_4, which avoid intermediate chloromethylquinolones (Scheme 6.84)[510].



Scheme 6.84

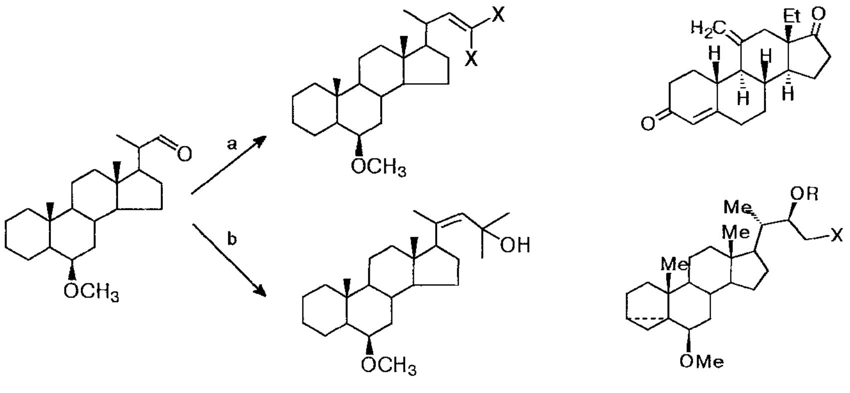
6.4.2.5 Steroids

The Wittig reaction is a important method for the synthesis and derivatization of steroids and has been employed extensively in terpene syntheses of polyenes used as precursors in the cyclization processes leading to steroids, especially elaboration of steroidal side chains by reaction with carbonyl groups at positions C-3, C-6, and C-17[a] and on the side chain[511-516]. The Wittig reaction of 4-pentenyltriphenylphosphonium bromide with estrone methyl ether gave the spirobicyclo[3,1,0]hexane (Eq. 6.199)[511]



(6.199)

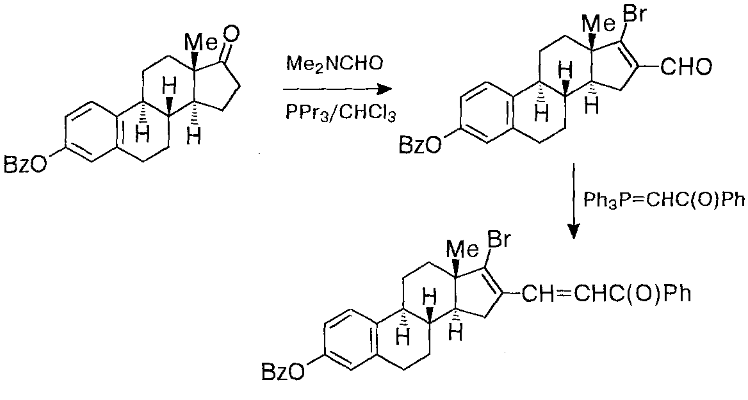
An improved synthesis of 13*β*-ethyl-11-methylenegon-4-en-3,17-dione was reported by Gao and coworkera[512]. A stereoselective approach to the brassinolide side chain via the Wittig reaction has also been reported[517]. Wittig reaction of the 22*R*-acetoxy compound furnished predominantly the 22*R*-hydroxy-2,3*Z* olefin which was further modified to form the brassinolide side chain. Salmond and coworkers[514] applied a stereoselective Schlosser–Wittig reagent to the synthesis of 25-hydroxylated Vitamin D metabolites and a number of other derivatives of 25-hydroxyholesterol. The *γ*-hydroxy ylide prepared from $Ph_3P{=}CH_2$ and butylene oxide reacted with steroidal aldehydes to give the Δ^{22}-25 product of *E*-configuration (Scheme 6.85):



a= $Ph_3P{=}CX_2$; b= $Ph_3P{=}CHCH_2CMe_2OLi$

Scheme 6.85

Thiemann and coworkers synthesized 3-(estran-16-yl)acrylates and 2-(estran-16-yl)vinyl ketones (Scheme 6.86) and studied their photochemical behavior to investigate the potential liquid crystalline behavior of C-16-substituted steroids[168].

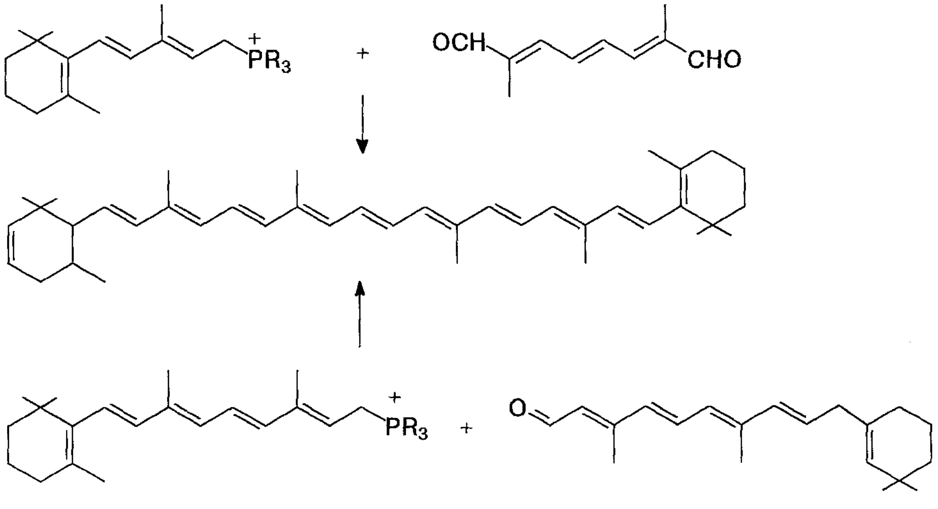


Scheme 6.86

6.4.2.6 Carotenoids, Retinoids, Polyenes

Owing to their extensive distribution in the plant and animal world the carotenoids stand out amongst the natural pigments. In their industrial production the Wittig reaction is a preferred process step for linking selected building blocks which are identical to those used in the synthesis of vitamin A, or are logically derived from these[518]. A review has been published on the Wittig reaction in the synthesis of carotenoids[518b].

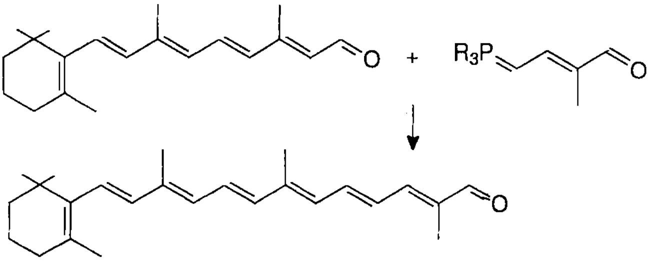
a) Terpenoids



Scheme 6.87

The Wittig reaction is undoubtedly one of the most useful methods in terpenoid chemistry[518-541] and most impressive results have been achieved in the synthesis of vitamin A and carotenoids. Some of these syntheses are used in industry. Carotenoids have important significance as foodstuff colorants with a natural structure and as anticancer drugs for inhibiting the uncontrolled growth of potential cancer cells, and thus as prophylactics against certain tumors[518,519]. BASF developed an industrial method for the synthesis of β-carotene, the orange-red colorant of carrot and the important provitamin A, based on linking two C_{15}-phosphonium salts with a C_{10}-dialdehyde in a double Wittig reaction ($C_{15} + C_{10} + C_{15} = C_{40}$ β-carotene) (Scheme 6.87)[520,521]. The C_{20}-retinyltriphenylphosphonium salt was obtained by reaction of triphenylphosphine with the acetate of vitamin A in the presence of an acid. The Wittig reaction of the salt with retinal-aldehyde results in β-carotene[522]:

Apo-carotenals and their corresponding carboxylates are natural colorants which occur in citrus fruits, spinach, and other plants and which possess the vitamin A activity. For their preparation appropriate building blocks must be connected with each other by means of Wittig reactions. Thus, β-apo-12′-carotenal (C_{25}) was obtained by reaction of C_{20} retinal with a C_5 phosphorus ylide (Scheme 6.88)[523,524]:

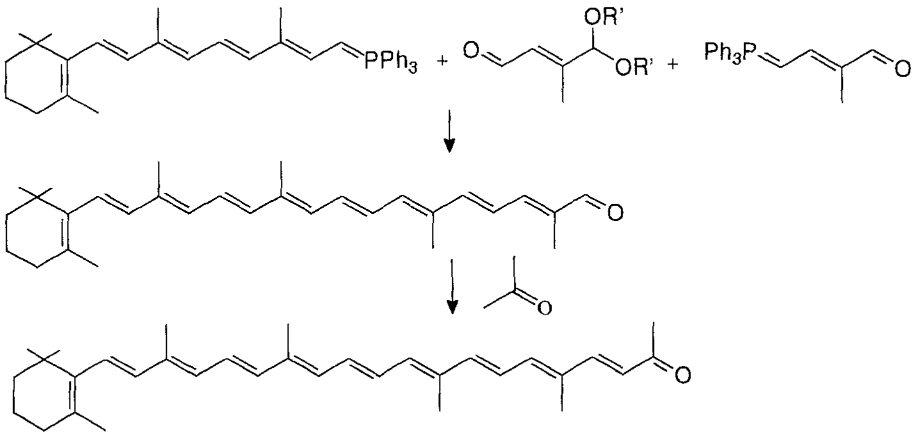


Scheme 6.88

Data have been published on several industrial variants of the synthesis of β-apo-8′-carotenal (C_{30}) (Scheme 6.89). β-Apo-8′-carotenal was obtained by reaction of a C_{20}-ylide with a C_5-dialkylmonoacetal and a C_5-ylide-al[523,524] and subsequently by reaction of a C_{15}-ylide with a C_{10}-dialkyl and a C_5-ylide-al[518]. β′-Apo-8′-carotenal was obtained by reaction of a C_{20}-retinal with two molecules of a C5-ylide-al[523,524] and also by reaction of a C_{20}-ylide with a dissymmetric C_{10}-dialdehyde (R′ = H). This reaction is remarkably regioselective because only one of the two aldehyde groups participates in the Wittig olefination with the formation of β-apo-8′-carotenal[527]. An aldol condensation of C_{30}-aldehyde with acetone leads to the formation of C_{33}-ketone citranaxanthine, which is used as a food-stuff colorant and feed additive. It has a reddish shade, similar to that of canthaxantine[526].

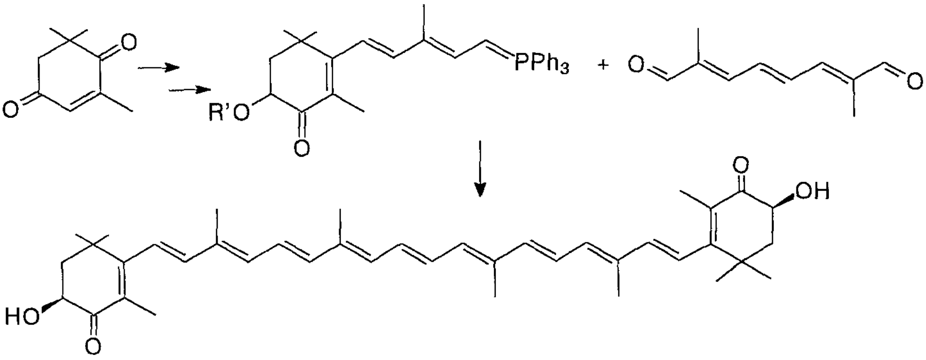
Ernst and Muenster published the short review describing the synthesis of β-apo-12′-carotenal and ethyl 8′-apo-β-caroten-8′-oate[527].

Canthaxanthine, which has a reddish color, is used as an feed additive. Astaxanthine is a chiral carotenoid occurring in the nature both in the optically active form, and in the racemic form[528,529].

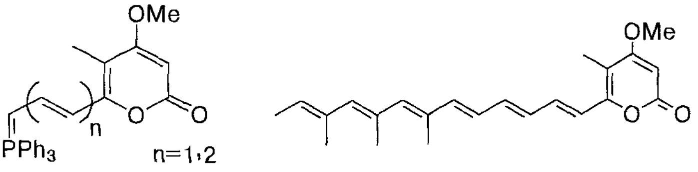


Scheme 6.89

Astaxanthine is a red pigment of lobster, salmon, and trout which also occurs in some green algae and yeast. Industrial syntheses of racemic (3*RS*,3'*RS*) astaxanthine have been developed; they are based on oxo-isophorone as starting compound. 3*RS*,3'*RS*-astaxanthine was obtained by Wittig reaction of a C_{15}-phosphorus ylide (R' = H) with dialdehyde (Scheme 6.90). Canthaxanthine is an oxidative metabolite of *β*-carotene[530].

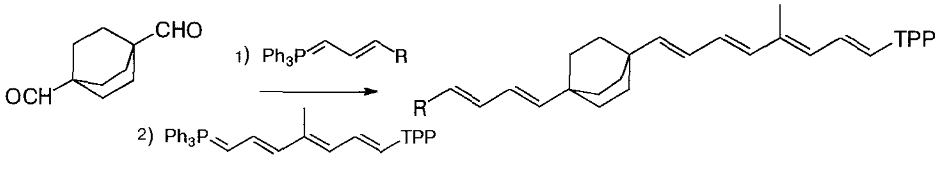


Scheme 6.90



Scheme 6.91

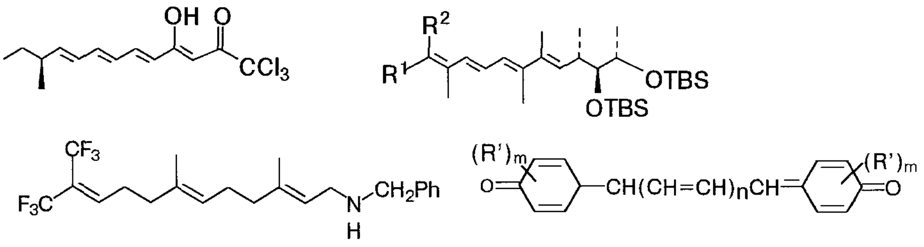
The Wittig reaction has been used in syntheses of carotenoid alkylidenebutenolides [533a] *E*-citreomontanin, (±)-citreoviral, (±)-citreoviridin, and aurovertins with related structures (Scheme 6.91)[534–536]:Ito et al. reported the synthesis of carotenoid analogues possessing fluorescence properties.[533b] Conjugated polyenes bearing a three-dimensional bicyclo[2,2,2]-octane group have also been obtained by the Wittig reaction (Scheme 6.92)[537];



R=9-antryl; TPP=2-tetraphenylporphyrinyl

Scheme 6.92

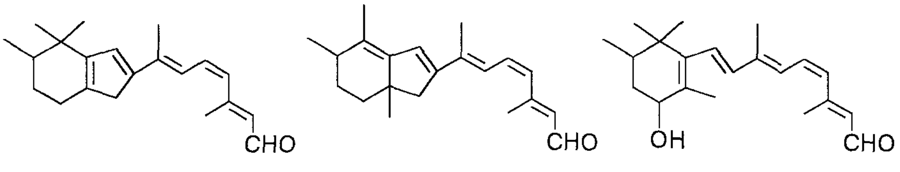
Phosphorus ylide olefination was used to build tetracene fragments of calyculins isolated from marine organisms (Scheme 6.96)[538]. Synthesis of the polyenone antibiotic neocarzilin A in the natural *S* configuration involves repeated use of a *ω*-reduction–oxidation sequence to construct the polyene chain.[539]. The bis (trifluoromethyl) analog, a powerful inhibitor of the squalene synthase, was synthesized using the Wittig reaction in a key step[540]. Japanese chemists have synthesized a food-stuff colorant which is a derivative of bis-2,5-cyclohexadiene-1 by the Wittig reaction (Scheme 6.93)[532]:



Scheme 6.93

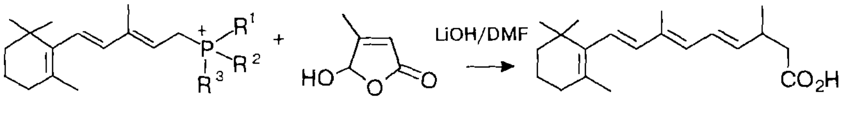
b) Retinoids

The Wittig reaction has been used extensively in retinoid chemistry.[541-548] It was, for instance, applied to syntheses of 6*S*-*cis*- and 6*S*-*trans*-169-bicyclic retinals[542] prepared from (+)-4*S*- and (–)-4*R*-11*Z*-4-hydroxyretinals (Scheme 6.94)[543]



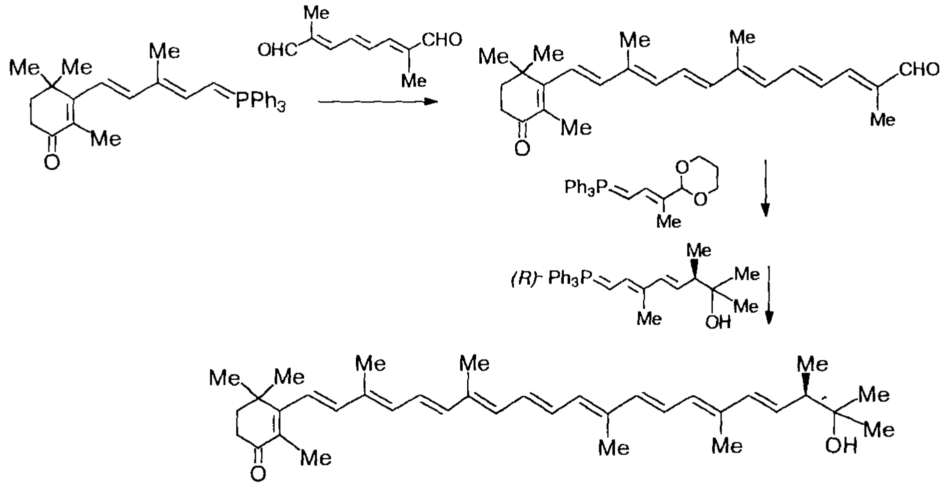
Scheme 6.94

13-*Z*-Retinoic acid was obtained in high yield by reaction of 5-hydroxy-4-methyl-2-(5*h*)-furanose with a triarylphosphonium salt in DMF in the presence of lithium hydroxide as a base with the subsequent partial photoisomerization of the reaction mixture of 13-*Z*- and 11,13-di-*Z*-retinoic acids[545]. The 9-*Z*-retinoic acid was prepared analogously (Eq.6.200) [546]:



(6.200)

Fluorinated retinals were synthesized by Wittig reaction and used as artificial pigments with near to normal absorption properties[541].



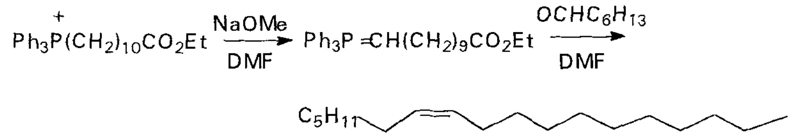
Scheme 6.95

Duhamel and co-workers described the synthesis of aldehyde-retinoids by the Wittig reaction[544]. γ-Jasmolactone, useful in perfume manufacture, was prepared by radical addition of the methyl ester of 3-formylpropionic acid to acrolein diethylacetal and by Wittig reaction resulting in 4-oxo-*cis*-decenoic acid methyl ester[547]. The synthesis of carotenoids in the Gilding bacterium Taxeobacter was described by Bircher and co-workers..[548] All-*E*, 2'*R*-3-deoxy-2'-hydroxyflexixanthin, was synthesized by a facile sequence of four consecutive Wittig reactions (Scheme 6.95)[548]:

c) Fatty Acids

The Wittig reaction has been widely employed for the synthesis of mono and polyunsaturated fatty acids and stereoselective techniques have enabled the preparation of very high (>95%) proportions of the naturally occurring *Z* isomers.

Unsaturated fatty acids occur naturally among the lipids of animals, higher plants, and microorganisms. Many higher Z-alkenoic acids have been synthesized by the Wittig reaction between a ω-alkoxycarbonyltriphenyl-phosphonium salt and an aliphatic aldehyde in strongly dipolar aprotic solvents such as dimethylformamide or dimethyl sulfoxide, using sodium methoxide and sodium hydride as bases. This procedure gives generally good yields of the alkenoic acid as the Z isomer in 90% stereochemical purity (Eq. 6.201):

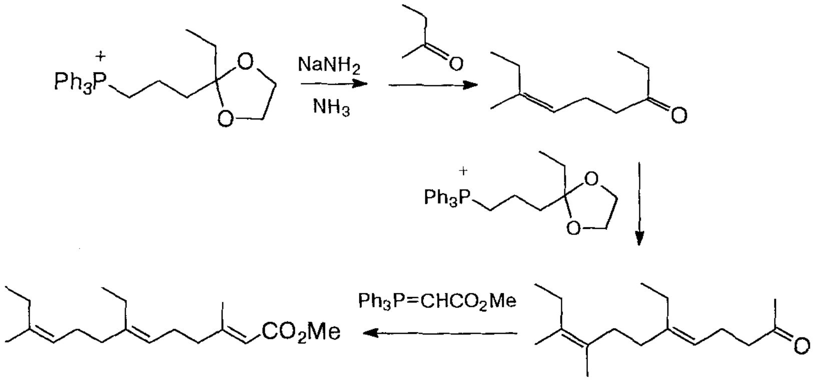


(6.201)

Many examples of fatty acid synthesis have been referred to in reviews by Bergelson[609], Gosney[608], Bestmann and Vostrovsky[601].

6.4.2.7 Juvenile Hormones and Pyrethroids

The considerable interest in the utilization of insect juvenile hormones as a highly effective means of plant protection is reflected in the growing number of synthetic approaches. An interesting example is the use of three consecutive Wittig reactions to build a the carbon skeleton of Juvocimene I[610a] and C_{18} juvenile hormone (Scheme 6.96):[610b]

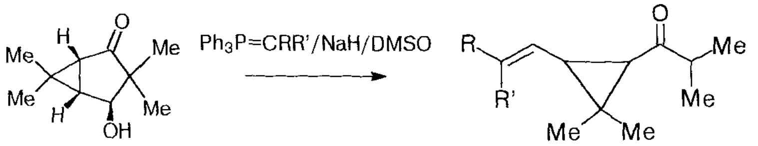


Scheme 6.96

Henrick made the most important contribution to the synthesis of juvenile hormones and juvenoids.[610d] Romanuk has reviewed this chemistry.[610e]

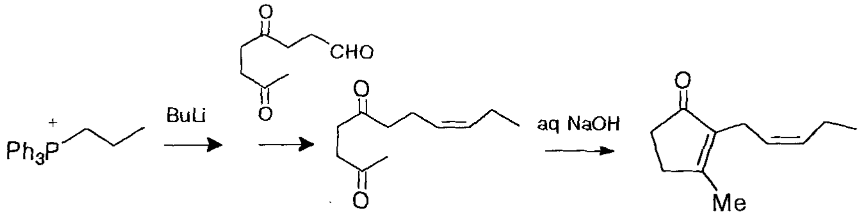
The great commercial demand for pyrethroid insecticides, which are both safe to mammals and biodegradable, has fueled the search for cheap and convenient synthetic routes to the important intermediates *trans*-chrysanthemic acid and its dihalo *cis* analogs (deltametrinic acid) and (cypermetrinic acid). The *gem*-dimethyl cyclopropyl unit in these acids can be incorporated by Wittig reaction of chiral α,β-unsaturated compounds and a phosphonium isopropylide. Much work has been performed on such a strategy by the use of triphenylphosphonium isopropylide in Krief's laboratory over the past 20 years[549].

A novel synthesis of vinylcyclopropyl ketones and vinylcyclopropane carboxylic acids has been applied to the synthesis of *trans*-chrysanthemic acid (Eq. 6.202):



(6.202)

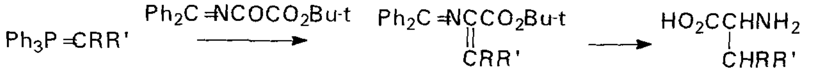
cis-Stereoselective Wittig reactions have also proved very suitable for the synthesis of cinerolone, jasmolone, and pyrethrolone (known collectively as rethrolones) which are the alcohol components of the insecticidal pyrethrin ester found in *Chrysanthemium cinerariaefolium*. The synthesis of the corresponding rethrone Z-jasmone, an important perfumery constituent, was prepared as shown in Scheme 6.97 by means of a stereoselective Wittig reaction[607]:



Scheme 6.97

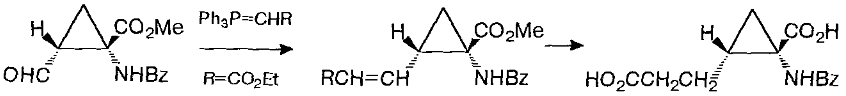
6.4.2.8 Amino Acids

The Wittig reaction has been used to prepare unique α-amino acids including optically active amino acids (See Section 6.2.3). Thus, the reaction of P-ylides with readily accessible oxalamides produced azadienes which were reduced to amino acids.(Eq. 6.203)[154]:



$$Ph_3P{=}CRR' \xrightarrow{Ph_2C{=}NCOCO_2Bu\text{-}t} \underset{CRR'}{\overset{}{Ph_2C{=}N\underset{\|}{C}CO_2Bu\text{-}t}} \longrightarrow \underset{CHRR'}{HO_2C\underset{|}{C}HNH_2} \qquad (6.203)$$

Cativella and coworkers proposed Wittig olefination as powerful tool for the synthesis of conformationally constrained cyclopropyl amino acids (Eq. 6.204)[550]:



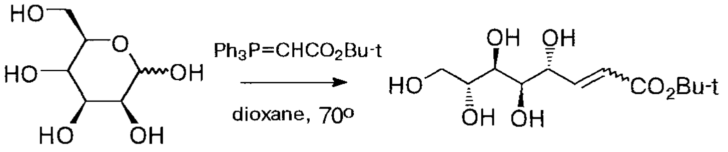
(6.204)

6.4.2.9 Carbohydrates

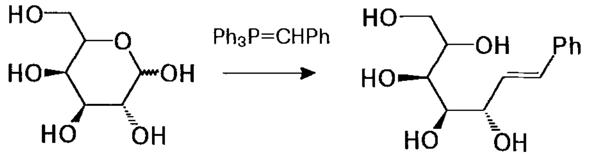
The Wittig reaction is a well investigated reaction in the carbohydrate field[552–575]. It is extensively used for derivatization of carbohydrates, important initial reagents in the synthesis of naturally occurring compounds.

Some recently reported examples of the reaction of phosphorus ylides with unprotected carbohydrates are shown in Eq. 6.205.[553] These compounds are useful intermediates in the synthesis of polyfunctional chiral compounds.

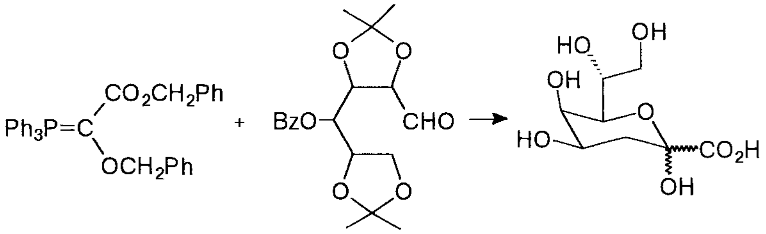
Henk and coworkers[552] studied the reaction of unprotected sugars with triphenylphosphonium benzylide leading to open-chain derivatives (Eq. 6.206).[552] The chain-elongated compounds were obtained in 66–72% yield by means of the Wittig reaction of D-galactose, D-glucose, D-arabinose or L-xylose with benzylide. Wittig reaction of triphenylphosphonium(benzyloxy)benzyloxy-carbonylmethylide with 4-*O*-benzyl-2,3:5,6-isopropylidene-D-mannose has been used to synthesize 3-deoxy-D-manno-2-octulosonic acid. (Eq. 6.207).[554] Stereoselective transformation leading to pentoso-1,4-lactones has been used as a step in a stereoselective synthesis of sphingosine and ceramide (Eq. 6.208)[556] and facile stereoselective synthesis of sphingosine and ceramide derivatives has been developed using D-xylose as chiral pool and a CuCN-catalyzed allylic alkylation reaction[557]. The reaction with acylylides proceeds analogously (Eq. 6.209)[557]:



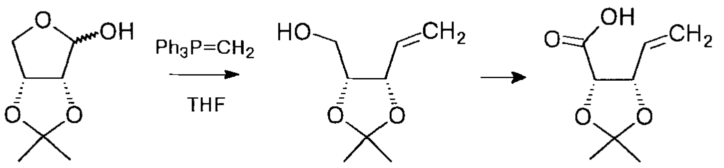
(6.205)



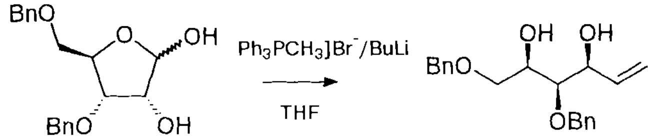
(6.206)



(6.207)

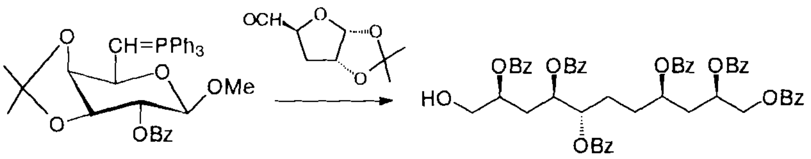


(6.208)



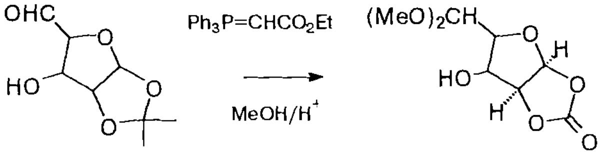
(6.209)

David and Malleron reported a new approach to a segment of amphotericin B, which was prepared by Wittig coupling of a glycoside with a deoxy sugar (Eq. 6.210)[558]:



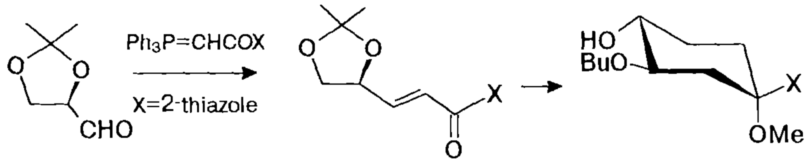
(6.210)

2-Deoxy-3,6-anhydrohexano-1,4-lactones, have been synthesized from aldehydosugars by the Wittig reaction followed by acid-catalyzed methanolysis and rearrangement (Eq. 6.211)[559]:



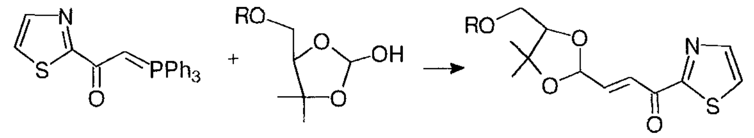
(6.211)

The Wittig reaction of 2-thiazolecarbonylmethylene ylide with D-glyceraldehyde and D-arabinose acetonides has been used as key step in the synthesis of new thiazole derivatives of carbohydrates (Eq. 6.212)[560]:

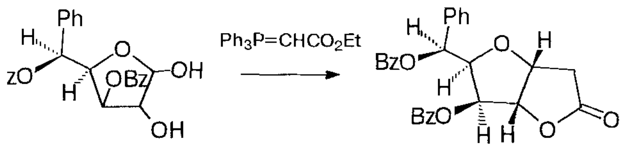


(6.212)

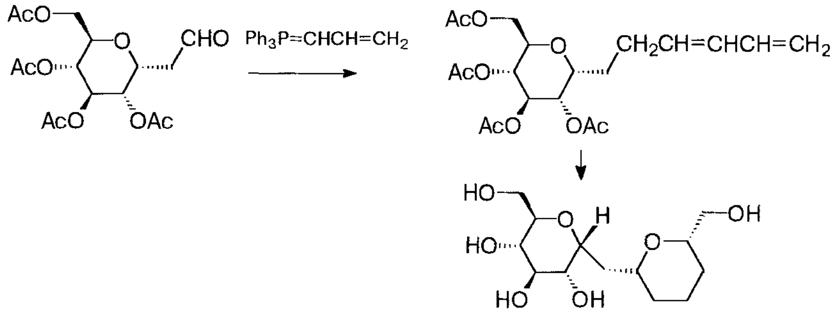
The reaction of 2-thiazolylcarbonylmethylenetriphenylphos with five protected D-furanoses leads to glycosides.[561] A thiazole-substituted carbonyl ylide has been used in a Wittig reaction to provide a masked α-ketoaldehyde function which has been applied to the synthesis of 3-deoxy-2-ulsonic acids[560] and α- and β-1-C-(2-thiazolacyl)-glycosides (Eq. 6.213)[561]. The reaction of phosphonium and arsonium ylides with aldoses, pyranoses and furanoses gives *E* alkene derivatives and the corresponding C-glycosyls[562a,b].

 (6.213)

The reaction of triphenylphosphonium ethoxycarbonylmethylide with furanose lactol is the key step in a new synthesis of the anti-tumor compound goneofufurone (Eq. 6.214)[563]:

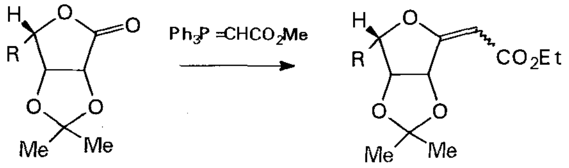
 (6.214)

New access to C-disaccharide analogs of α,α-trehalose was developed using aqueous hetero Diels–Alder reaction and Wittig reaction.(Scheme 6.98)[564]:

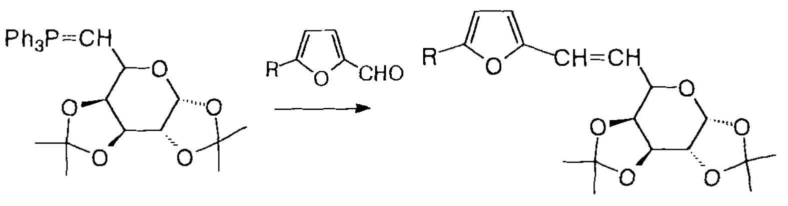


Scheme 6.98

Direct olefination of lactones, derived from sugars, with stabilized phosphoranes proceeds at 140°C in an autoclave with good to excellent yields (Eq. 6.215)[565]:

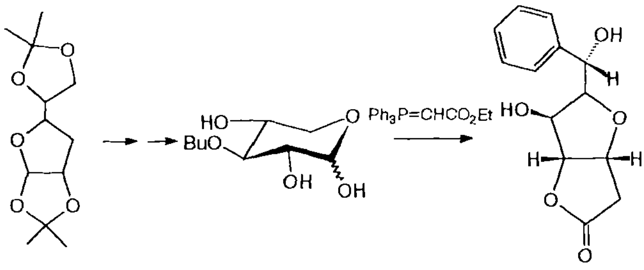
 (6.215)

E and *Z* isomers of heterocyclic compounds with saccharide components, and P-ylide derivatives of saccharides, have been prepared by the Wittig reaction[567–570]. Hansen reported the synthesis of first 1-azaanalogs of α-sugars (Eq. 6.216)[571]:



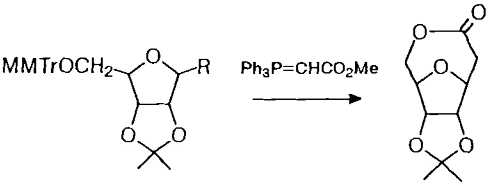
(6.216)

(–)-*Epigoniofufurone*, isolated from the stem-bark of *Thaigoniothalamus*, was synthesized very efficiently in six steps from diacetone glucose (Scheme 6.99)[572]

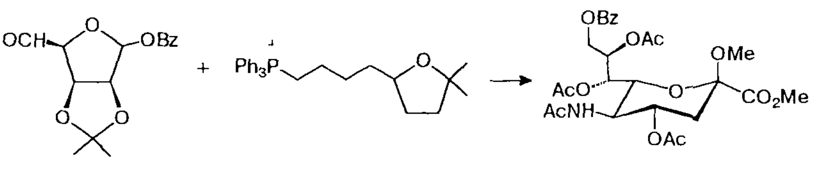


Scheme 6.99

Mandal and Achari reported that the Wittig reaction of β-D-ribofuranose with triphenylphosphonium methoxycarbonylmethylide was accompanied by spontaneous cyclization to generate I stereospecifically. Deprotonation in situ followed by mild basic hydrolysis and cyclization with Py-Ac$_2$O-DBU then yielded an hydrotetrahydroxyoxocanone in good overall yield (Eq. 6.217)[573b]:
N-acetylneuraminic acid has been prepared via *cis*-selective Wittig reaction of lyxopentodialdose with a phosphonium salt in the presence of NaN(SiMe$_3$)$_2$ as base (Eq. 6.218)[574]:



(6.217)

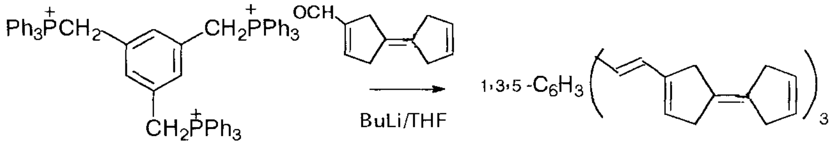


(6.218)

Recent development in the synthesis of C-glycosides via Wittig reaction and palladium catalyzed Huck type coupling reactions has been reviewed.[575]

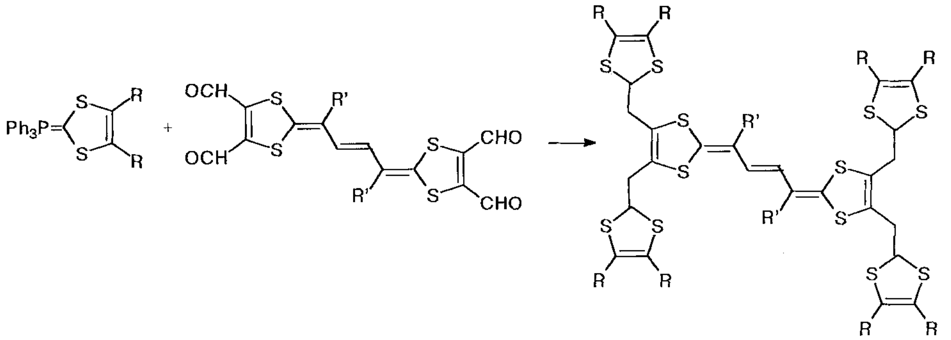
6.4.2.10 Tetrathiafulvalenes

Phosphorus ylide olefination is widely used in the synthesis of tetrathiafulvalenes (TTF); these compounds have the properties of organic semi-conductors, and thus important practical applications[576–588]. 1,3,5-analogs of 1,3,5-triacylbenzenes are obtained by Wittig olefination of the tris-ylides of 1,3,5-substituted benzene (Eq. 6.219)[579–580]:



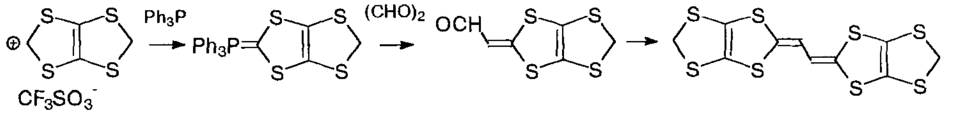
(6.219)

Tetrathiafulvalene vinylogs have been synthesized by tetra-Wittig reaction of tetraaldehyde[580] with TTF donors bearing methylene steric groups, prepared from bisphosphonium salts (Scheme 6.100)[581]:



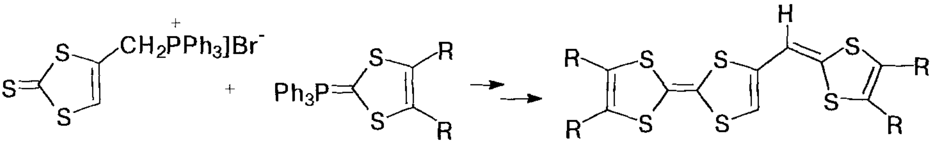
Scheme 6.100

Some other electron-donor tetrathiofulvalene vinylogs were obtained analogously (Eq. 6.220)[582,583]:



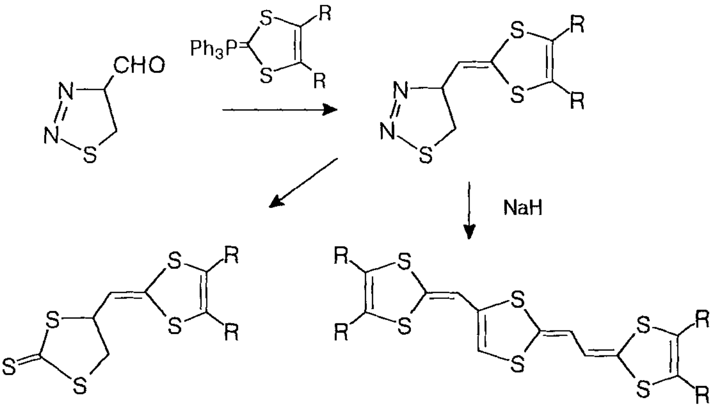
(6.220)

Nozdrin and coworkers synthesized a Wittig reagent useful in 1,3-dithiol and TTF chemistry and applied it for the syntheses of a number of new highly conjugated donors of π-electrons by combining TTF and 2,2'-ethanediylidene-bis-(1,3-thiol) fragments (Scheme 6.101)[584,585]:



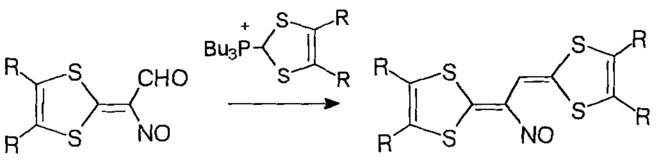
Scheme 6.101

Mild and efficient synthesis of new vinylogs of tetrathiafulvalene π-donors via Wittig reaction. and base-catalyzed ring opening have been described. The compounds have lower oxidation potentials than the already known organic superconductor bis(ethylenedithiol)tetrathiafulvalene (Scheme 6.102)[586]:



Scheme 6.102

Jackson and co-workers have reported the synthesis of nitroso derivatives of vinylogous tetrathiafulvalene, the first examples of this class of compound (Eq. 6.221)[587]:



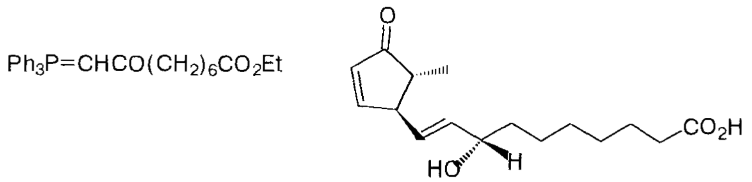
(6.221)

Ylides containing an en-yn function, starting compounds in the synthesis of a fulvalene system bearing large (13- and 15-membered) rings, have also been reported[588].

6.4.2.11 Miscellaneous

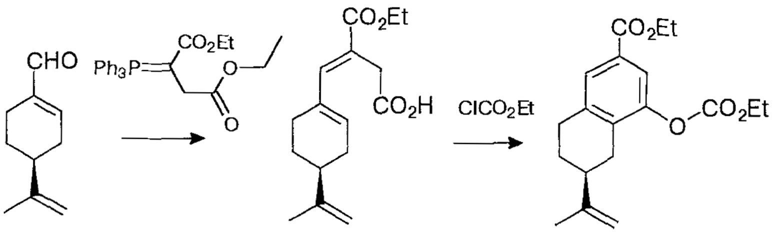
The Wittig reaction has made a significant contribution to the synthetic approaches which have made important substances available in reasonable quantities.[589-600] The

Wittig reaction has been used to introduce an exocyclic double bond, with exclusively *E* stereochemistry, in a synthesis of the racemate of a natural algal-growth inhibitor[589]. The reaction of triphenylphosphonium alkylides with *ω*-oxoesters has been used as a route to the *cis* isomers of very-long-chain fatty acid methyl esters (Scheme 6.103)[590]:



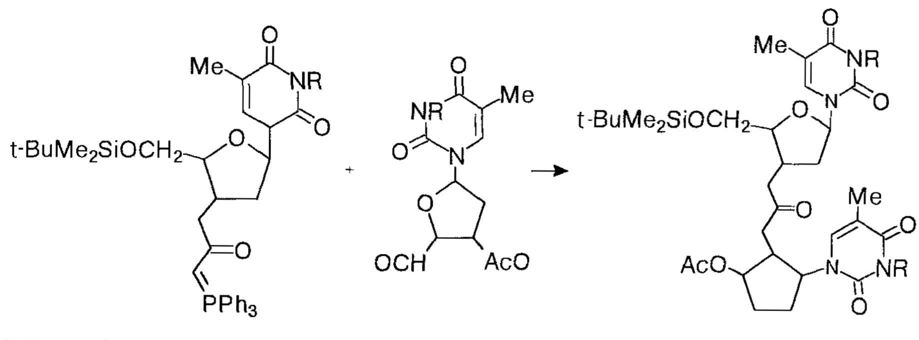
Scheme 6.103

A new and facile method for the synthesis of chirally substituted tetrahydronaphthalenes as suitable skeletons in terpene synthesis has been presented by Brenna and coworkers (Eq. 6.222)[596]:



(6.222)

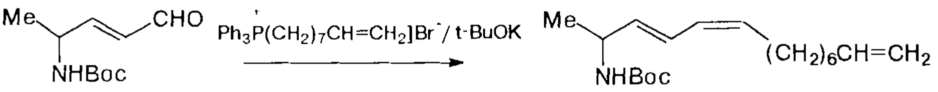
Butterfield and Thomas[598] condensed a keto-ylide and an aldehyde monohydrate to prepare a dinucleotide analog (Scheme 6.104):



Scheme 6.104

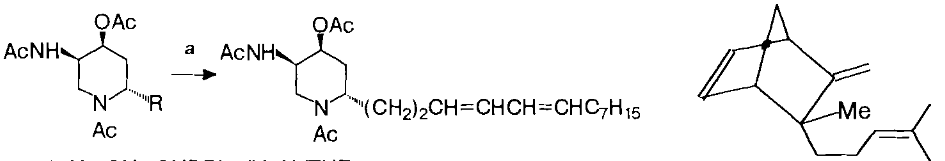
2*S*,3*E*,5*Z*-2-amino-3,5,13-tetradecatriene, which has both cytotoxic and antifungal properties, has been synthesized for the first time by the Wittig reaction of an *S*-*γ*-

aminoenal with an unsaturated phosphonium salt in the presence of potassium *tert*-butoxide (Eq. 6.223)[593]:



(6.223)

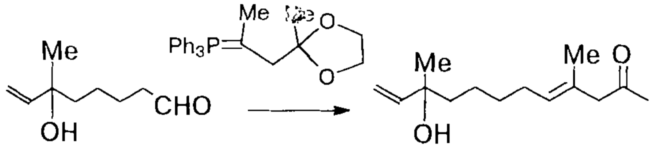
The first total synthesis of (+)-calyculin A was achieved using a *E*-stereoselective Wittig coupling of the C_1–C_{25} and C_{26}–C_{37} sub-units (Scheme 6.105)[591] and a Wittig reaction involving triphenylphosphonium dec-2-enylide has been used to prepare the acetates of a structure previously suggested for pseudodistomins A and B[592]. The Wittig reaction was also used in the synthesis of ent-β-santalene, a constituent of sandalwood[597].



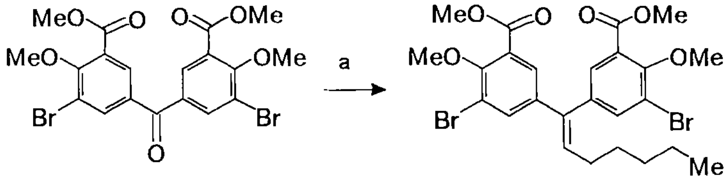
a= $C_7H_{15}CH=CHPPh_3$/NaH/THF

Scheme 6.105

Interest in preparing biologically active compounds via the Wittig reaction arose quite early with the synthesis by Tolstikov et al. of equinolone (Eq. 6.224)[594]—an interesting example of the preparation of a biologically active compound. The preparation of a non-nucleoside inhibitor of HIV-1 reverse transcriptase has been reported by Gushman (Eq. 6.225)[595]:



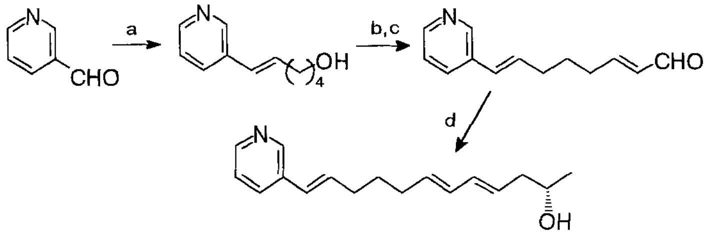
(224)



(225)

a=$Ph_3P(CH_2)_5CH_3]Br^-/NaN(SiMe_3)_2$[595]

Matikainen and coworkers reported interesting example of the synthesis of Haminols A and B, which have antileukemic activity, as a result of three consecutive Wittig reactions (Scheme 6.106).[596] [184b]



a = $Ph_3P(CH_2)_5OH + K_2CO_3$, *hv*; b = CrO_3; c = $Ph_3P{=}CHCHO$;
d = $Ph_3P(CH_2)_2CH(OH)Me]Br + BuLi$

Scheme 6.106

The use of the Wittig reaction in the synthesis of ethyl *Z*- and *E*-octa-2,6-dienopyranosiduronates has been reported by Gomes and co-workers[599].

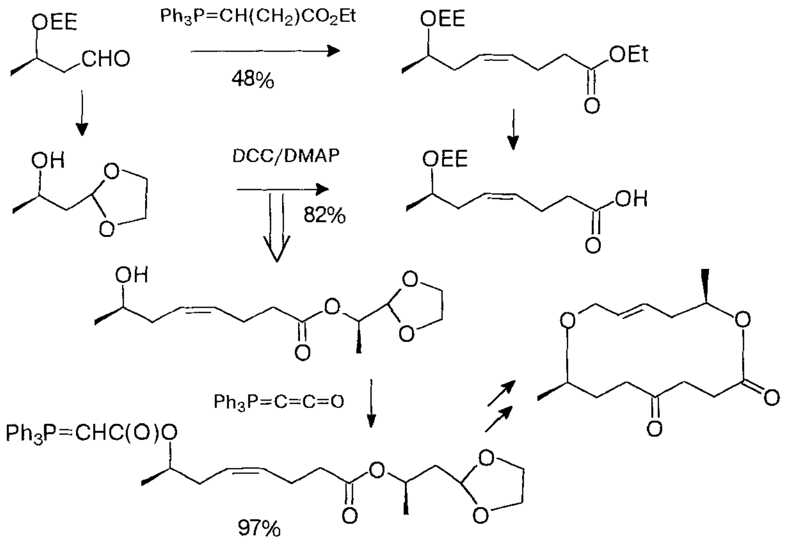
One step Wittig olefination of methyl pyroglutamate has been used in the chiral synthesis of 5*S*-alkenyl-2-pyrrolidinones and *S*-vigabatrin and an effective methodology for the enantioselective preparation of these compounds was developed[600].

6.4.3 Total Synthesis Involving the Wittig Reaction

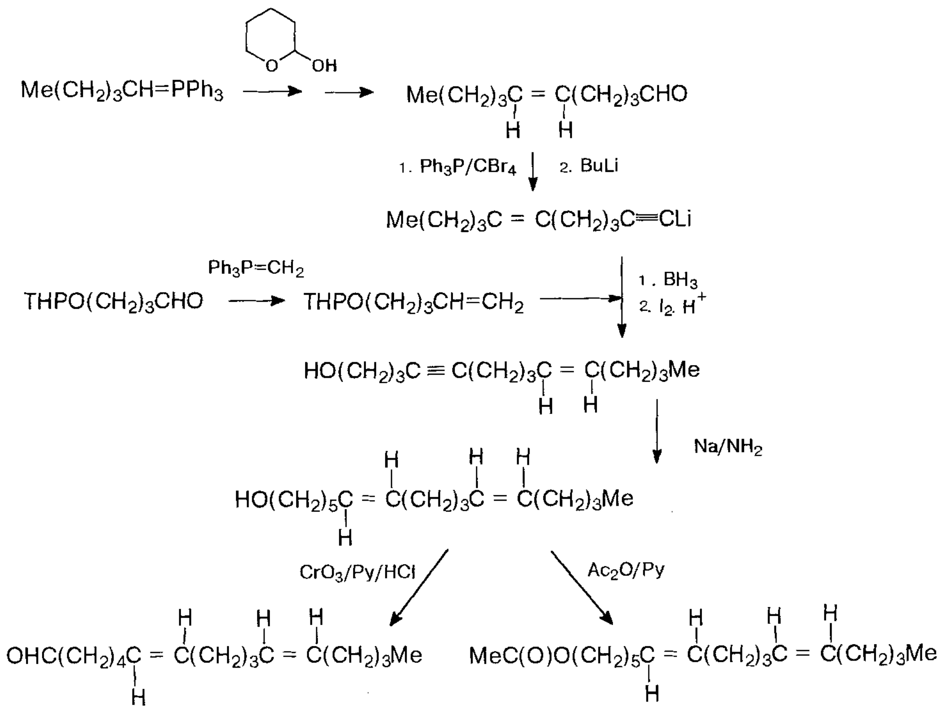
The power of the Wittig reaction and related reactions in chemical synthesis is amply demonstrated by the widespread application of these process in the total synthesis of complex products. Many examples of the application of the total syntheses of natural products involving the Wittig reaction can be found elsewhere[273,275,343,518,601-603]. Because of the enormous task involved in ensuring complete coverage of the literature we only select several examples of the application of such reactions.

The preparation of the naturally occurring optically active macrocyclic compound grahamamycin is an example of such a total synthesis. The protected acetaldol reacts with ylide to form an olefin with a protected alcohol function. After de-esterification the unsaturated acid was obtained. Simultaneously the acetaldol was converted to an alcohol with a protected aldehyde function and the condensation of the acid with the alcohol results in new alcohol which was reacted with ketene ylide to give the acyl ylide. The protecting group of latter was cleaved in acid medium and the resulting aldehydo-ylide readily participates in an intramolecular Wittig reaction to form optically active (–)-grahamamycin (Scheme 6.107). The physical, spectroscopic and biological properties of the product were identical with those of natural grahamamycin[92,93].

The total synthesis of some pheromones is based upon the achievements of contemporary synthetic organic chemistry, including the Wittig reaction. Thus the multi-step synthesis of 6*E*,11*Z*-hexadecadienylacetate and hexadecadienal, sex-attractant pheromones of the female moth *Antheraea polyphemus* was proposed by Bestmann and Li (Scheme 6.108)[420]. These compounds were synthesized by a combining the Wittig reaction with acetylenic and organoboron chemistry.



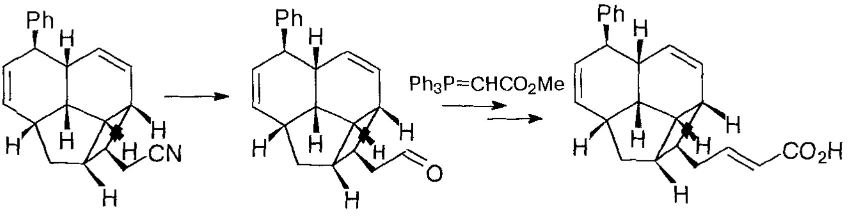
Scheme 6.107



Scheme 6.108

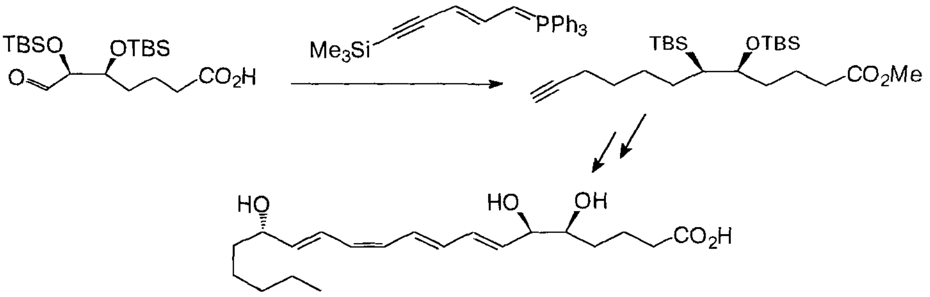
The *Z* enol prepared by the Wittig reaction was acidified to give the unsaturated aldehyde and then treated consecutively with triphenylphosphine and carbon tetrabromide. The product was reacted with butyllithium and transformed into lithium acetylide. Wittig reaction of the aldehydoalcohol with a protected OH-group furnished the olefin and this was transformed by reaction with borane and then iodine into the *Z*-en-yne. Further treatment with sodium in liquid ammonia produced the 6*E*,11*Z*-hexadecadienol. Oxidation of this with chromium oxide in pyridine led to the formation of 6*E*,11*Z*-hexadecadienal whereas acylation with acetic anhydride in pyridine led to 6*E*,11*Z*-hexadecadienyl acetate.

In 1982 Nicolaou and coworkers described the total synthesis of a class of naturally occurring compounds known as endiacric acids. In this synthesis the cyanide derived from 2*E*,4*Z*,6*Z*,8*E*-deca-2,4,6,8-tetraene-1,10-diol served as the common intermediate After standard transformations the tetracyclic aldehyde was subsequently converted into entiandric acid by Wittig reaction with the triphenylphosphonium carbomethoxymethylide and hydrolysis of the ester (Scheme 6.110). [604].



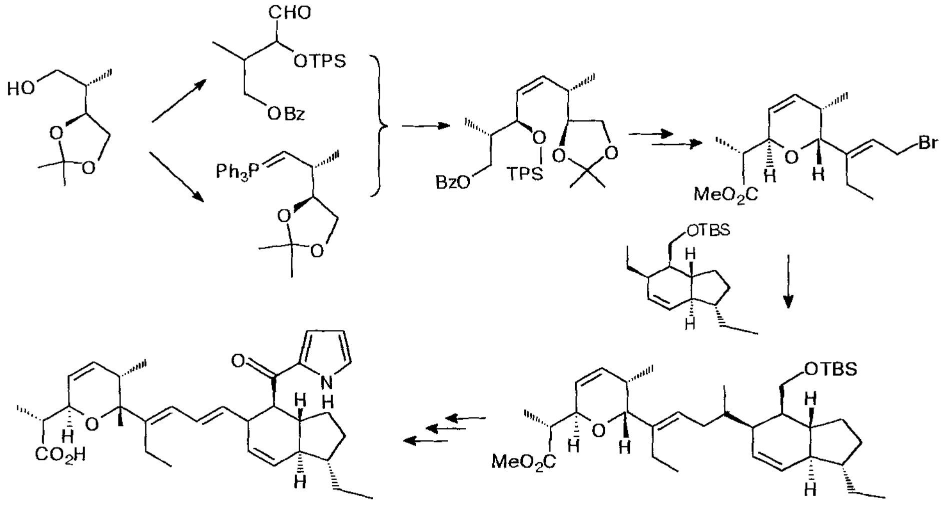
Scheme 6.110

The Wittig reaction was used in the total synthesis of lipoxin A4[605]. Alkoxy or silyloxy-substituted aldehydes reacted with the phosphonium en-yne ylide to give a 1:1 mixture of the *Z* and *E* alkenes in a combined yield of 98%. The *Z* isomer can easily be converted to the desired *E* isomer by treatment with a catalytic amount of iodine (Scheme 6.111).



Scheme 6.111

An alcohol served as the starting material for both the carbonyl component and the phosphoranylidene of a Wittig reaction applied in the total synthesis of the ionophore antibiotic X-14547 A (Scheme 6.112). Because of the effect of α substituents on the Wittig reaction, the olefin was obtained as a mixture of stereoisomers (*Z*:*E* = 1:2). The double bond was hydrogenated in a later stage of the synthesis[606].



Scheme 6.112

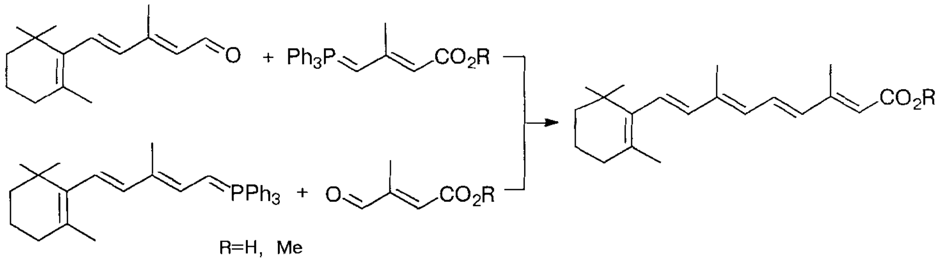
6.4.4 Industrial Application of the Wittig Reaction

A short time its discovery the Wittig reaction was used by scientists at the BASF plant in Ludwigshafen for the preparation of retinoic acid from a phosphorus ylide and an aldehyde. At this time industry had been actively seeking methods of producing synthetic and naturally occurring compounds (vitamins and carotenoids) for the foodstuff market. Within a few years a continuous process capable of producing 600 tons of vitamin A per year had been developed on the basis of the Wittig reaction.[611] Owing to the accessibility of the starting compounds, the simplicity of operations, and the high yields of olefins, the Wittig reaction has been widely applied for the industrial synthesis of carotenoids and the vitamin A. Industrial applications of the Wittig Reaction were reviewed by Pommer in 1977[442].

6.4.4.1 Synthesis of Vitamin A

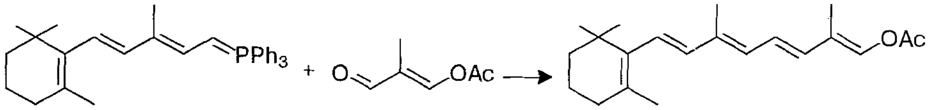
The first commercial application of the Wittig reaction was the synthesis of vitamin A by the BASF plant. Vitamin A has important biological significance—it participates in the differentiation of epithelial tissue, growth, and reproduction and in the process of sight in mammals, including man.

At the beginning of 50s work aimed at developing an industrial synthesis of vitamin A was begun at BASF research[20,611]. In 1953 G. Wittig and Geisler discovered the reaction of olefination of carbonyl compounds by phosphorus ylides. Owing to the traditionally close contact between University professors and industrial chemists in Germany, Wittig's discovery was immediately known in the BASF laboratories and Reppe and Pommer immediately recognized its significance for the synthesis of vitamin A. They invited G. Wittig to their laboratory and after only a few days discussion the synthesis of retinoic acid was achieved (Scheme 6.113).



Scheme 6.113

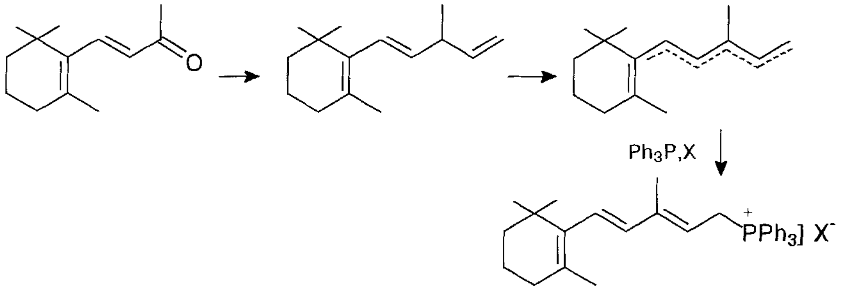
Pommer, Reppe, and Wittig then created an industrial method for the synthesis of vitamin A in which a C_5 carbonyl compound was reacted with a C_{15} phosphorus ylide (Eq. 6.226)[518]:



(6.226)

The Wittig reaction was then adapted for use under industrial conditions. Thus, organolithium compounds were successfully replaced by alcoholates and used as solutions in alcohols. Later the Wittig reaction was performed in an aqueous environment, under-phase transfer conditions[171]. In this way it was discovered that this type of stabilized ylide is hydrolytically stable and is very slowly hydrolyzed at temperatures below +5°C. The problem of the considerable positive heat effect was successfully solved by conducting the reaction continuously in a small reaction volume and conducting the heat away adiabatically[612,613].

A new method was developed for the synthesis of the phosphonium salts. The reaction of alcohols with acids generated a carbocation which alkylated phosphine with the formation of the phosphonium salts. This method was suitable for industrial synthesis of the C_{15} phosphonium salt from β-ionone which was converted into β-vinylionol. Reaction of the β-vinylionol with triphenylphosphine in the presence of acid, via the formation of carbocation, resulted in the phosphonium salt used as the initial C_{15} building block of vitamin A (Scheme 6.114)[613–617]

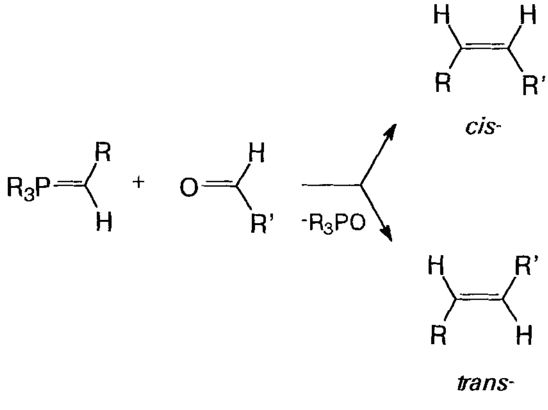


Scheme 6.114

In the industrial synthesis the natural all-*trans* isomer of vitamin A acetate was formed in 70% yield and was separated by crystallization from heptane. To avoid losses the 9-*cis* or 11-*cis* isomers can be rearranged into the all *trans* isomer by use of *cis–trans* isomerization catalysts, such as iodine or palladium complexes, and photochemical isomerization with ultraviolet light[613] or thermal isomerization[618].
Preparation of olefins by the Wittig reaction has been patented[618]. *p*-Nitrobenzyl-triphenylphosphonium ylide has been used as a chain-transfer agent for copolymerization of methyl methacrylate with styrene[620]. The preparation of 9-formyl-10-(*p*-nitrostyryl)anthracene by selective Wittig reaction of 9,10-diformylanthracene with *p*-nitrobenzyl triphenylphosphonium halide in the presence of an alkali metal salt in a polar solvent has also been developed [620].

6.5 Stereochemistry of the Wittig Reaction

The Wittig reaction results in *cis* and *trans* alkenes, the ratio of which depends on the structures of starting compounds, the reaction conditions, solvents, and various additives (Scheme 6.115). The possibility of actively controlling the stereochemistry of the Wittig reaction has great practical significance, because usually only one geometrical isomer of olefins is biologically active. When the Wittig reaction was originally discovered, and there was no understanding of its mechanism, it was impossible to clarify the factors affecting the stereochemistry of the formation of alkenes. In recent years the mechanism and the stereochemistry of the Wittig reaction have been intensively studied[12,343,608,622,623].



Scheme 6.115

The stereochemistry of the Wittig reaction has been reviewed several times, the most thoroughly by Vedejs (in 1996)[623] and Maryanoff and Reitz (in 1989)[705]. This section provides an overview of the stereochemistry of the Wittig reaction, including its scope and the variety of new classes of compounds.

6.5.1 Effect of Structural and Reaction Variables on the Stereochemistry

The ratio of *cis* to *trans* olefins formed in the Wittig reaction depends strongly on the activity of ylide and the reaction conditions (in particular the nature of the solvent). The stereoselectivity of the Wittig reaction with P-ylides generally favors one isomer and shifts from *E* to *Z* according to the stability of the ylide. Reaction of so-called 'non-stabilized' triphenylphosphonium ylides with an aldehyde results in the preferential formation of the contrathermodynamic *Z* alkene[622].

The Table. 6.16 shows the effect of reaction medium and ylide structure on the *Z*:*E* alkene ratio for trialkyl- and triphenylphosphonium ylides. This table summarizes the most significant results of recent publications[529,624–628].

6.5.1.1 Stereochemistry of Stabilized Ylides

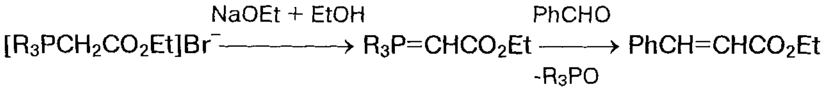
The Wittig reactions of stabilized ylides with aldehydes and with unsymmetrical ketones leads stereoselectively to the preferential formation of *E* olefins. The stereoselectivity of the reaction depends on the substituents on the phosphorus and carbon atoms of the P=C group. The replacement of phenyl groups on the phosphorus by alkyls, increases the *E*-stereoselectivity of the Wittig reaction (Eq. 6.227, Table 6.17, ethanol as a solvent)[629].

Table 6.16. Effect of reaction medium and ylide structure on the *Z*:*E* alkene ratio

$R^1_3P{=}CHR^2 + R^3CHO \rightarrow R^2CH{=}CHR^3 + R^1_3PO$

R^1	R^2	*Z*:*E* alkene ratio in: Aprotic solvents	Protic solvents
Ph	H, Alk (non-stabilized ylides)	$Z > E$	$Z > E$
Ph	Ar, $CH{=}CH_2$ (semi-stabilized ylides)	$Z \approx E$	$Z \approx E$
Ph	COH, COR, CO_2R, CN, SO_2R (stabilized ylides)	$Z < E$	$Z < E$
Alk	Alk, Ar, electron acceptor	$Z < E$	$Z < E$

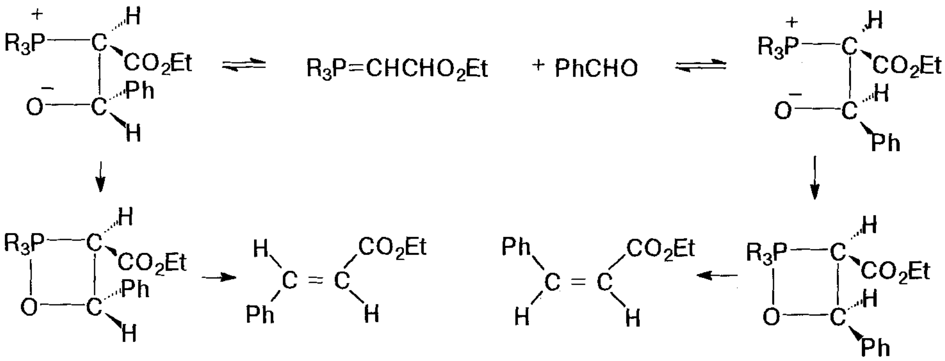
The effect of substituents on the phosphorus atom on the stereochemistry of the Wittig reaction can be explained by Bestmann's mechanism. The initial step of the reaction of triphenylphosphonium carboethoxymethylide with aromatic aldehydes is the formation of *threo* and *erythro* betaines, existing in equilibrium. The *threo* betaine is more thermodynamically stable, because of steric hindrance between the aryl and carboethoxy groups (Scheme 6.116).[630] Evidently, a high positive charge on the phosphorus accelerates the conversion of betaine into olefin and the equilibrium between the betaine isomers shifts toward the thermodynamically more favorable *threo* isomer to result in the formation of the *trans* olefin.



$$[R_3PCH_2CO_2Et]Br^- \xrightarrow{NaOEt + EtOH} R_3P{=}CHCO_2Et \xrightarrow[-R_3PO]{PhCHO} PhCH{=}CHCO_2Et \qquad (6.227)$$

Table 6.17. Effect of the substituent R on the *Z*:*E* alkene ratio of the Wittig reaction (Eq. 6.227)

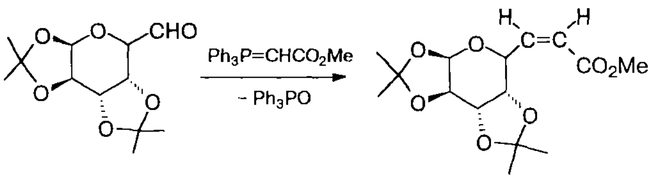
R	*E* (%)	*Z* (%)	Ref.
Ph	15	85	313,629
Bu	5	95	313,629
n-C_6H_{13}	2	98	629
n-$C_{10}H_{21}$	4	96	629
c-C_6H_{11}	0	100	630



Scheme 6.116

The Wittig reaction of stabilized ylides usually furnishes *E* olefins in high stereochemically purity. For instance, the reaction of triphenylphosphonium carboethoxyethylide with acetaldehyde affords a 3.5:96.5 mixture of the *Z* and *E* isomers of the methyl ester of tiglic acid[631–635].

The stereoselectivity of the Wittig reaction depends strongly on the reaction medium. The reaction of stabilized ylides with aldehydes furnishes the highest amount of the *trans* olefin in non-polar aprotic solvents. In protic solvents and aprotic solvents containing dissolved Lewis acids (lithium salts), the proportion of *cis* olefins increases[93]. Valverde and coworkers[636] showed that the stereoselectivity of the reaction of triphenylphosphonium methoxycarbonylmethylide with various alkoxyaldehydes varied from very high (*Z*:*E* isomer ratio >99:1) in methanol to modest (*Z*:*E* ratio 1:2) in dichloromethane . The stereoselectivity of the reaction also depends on the temperature. Thus, the *Z*:*E* alkene ratio at –8°C was 100:1, and at the room temperature was 3.2:1 (Eq. 6.232, Table. 6.17):

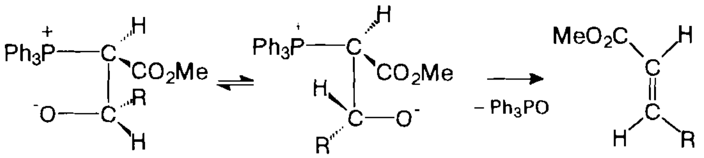


(6.228)

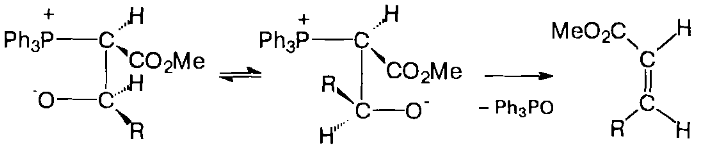
Table 6.18. Effect of solvents and temperatures on yields and Z/E alkene ratio (Eq. 6. 228) [636]

Solvent	Temp.°C	Yield (%)	*Z*:*E* ratio
i-PrOH	25	50	10:1
EtOH	25	48	22:1
MeOH	0	60	35:1
MeOH	-8	68	100:1
MeOH	24	82	37:1
$C_6H_5CH_3$	24	81	1:1
CH_2Cl_2	24	80	1:2

Solvation of the negatively charged oxygen atom of the betaine with the appropriate acid probably affects the stereoselectivity by reducing the electrostatic attraction of the charged centers of betaine; this enables the existence of *syn*-periplanar conformations, thus slowing down the rate of the betaine decomposition (Eq. 6.229, 6.230)[163,637]:

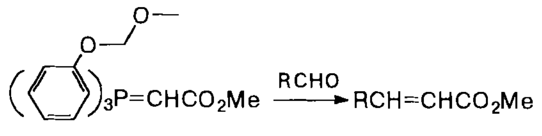


(6.229)



(6.230)

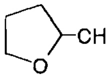
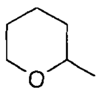
The presence of Lewis acids in the reaction medium increases the *Z*:*E* isomer ratio and accelerates the formation of alkene[162,163]. Patil and Schlosser recently proposed a reagent for controlling the *Z*:*E* selectivity of Wittig olefination of ketones (Eq. 6.231, Table 6.18)[40]



(6.231)

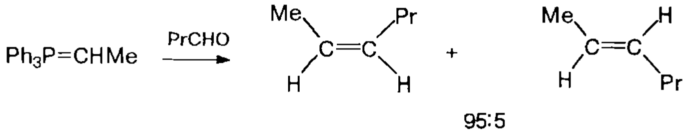
A curious solvent effect is observed for 2-tris(methoxymethoxyphenyl)phosphonium carbomethoxymethylide. When methanol was used as a solvent it reacts with saturated and unsaturated, α-alkoxy-α,β-unsaturated and α-alkoxy-substituted aliphatic aldehydes to produce α,β-unsaturated esters with very high *cis*-selectivity. In hexane *trans* isomers are obtained preferentially.

Table 6.19. Z:E selectivity of 2-Tris(methoxymethoxyphenyl) phenyl)phosphonium carbomethoxymethylide (Eq. 6.231)[40]

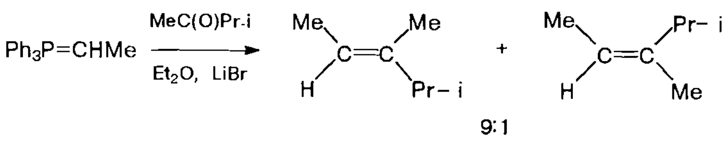
	Z:E	
R	MeOH	C_6H_{14}
i-Pr	91:9	5:95
t-Bu	82:18	63:37
$MeOCH_2$	91:9	28:72
	95:5	15:85
	91:9	11:89

6.5.1.2 Non-stabilized Ylides

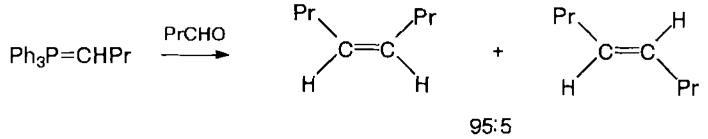
Unlike the Wittig reaction of stabilized ylides, which preferentially affords *E* alkenes, the Wittig reaction of non-stabilized ylides with carbonyl compounds leads to the formation of the thermodynamically less favorable *Z* alkenes (Eq. 6.232–6.234)[639 641].



(6.232)



(6.233)



(6.234)

The stereoselectivity of the reaction of non-stabilized ylides with carbonyl compounds depends on the reaction conditions. Lithium salts have little effect on the stereochemistry of the reaction of non-stabilized ylides with carbonyl compounds in the dipolar aprotic solvents dimethylformamide[641], dimethyl sulfoxide[641-644], and hexametapol[639,645]. Under these conditions non-stabilized ylides afford a mixture of olefins containing approximately 90% of the *Z* isomer both in the presence and in the absence of lithium salts (Table 6.20, Eq. 6.235, 6.236). Addition of DMSO, HMPTA, or co-solvents to THF promotes the formation of *Z* olefins (Eq. 6.241).[646]

$$[\mathrm{Ph_3\overset{+}{P}CH_2Et}]\mathrm{Br}^- \xrightarrow{\mathrm{BuLi}} \mathrm{Ph_3P{=}CHEt} \xrightarrow{\mathrm{EtCHO}} \underset{Z:E\ 95:5}{\mathrm{EtCH{=}CHEt}} \tag{6.235}$$

$$[\mathrm{Ph_3\overset{+}{P}CH_2R}]\mathrm{Br}^- \xrightarrow[\mathrm{(Me_2N)_3PO}]{\mathrm{2K}} \mathrm{Ph_3P{=}CHR} \xrightarrow{\mathrm{R'CHO}} \underset{Z:E\ 95:5}{\mathrm{RCH{=}CHR'}} \tag{6.236}$$

$$[\mathrm{Ph_3\overset{+}{P}CH_2C_7H_{15}}]\mathrm{Br}^- \xrightarrow{\mathrm{NaCH_2SOMe}} \mathrm{Ph_3P{=}CHC_7H_{15}} \xrightarrow{\mathrm{t\text{-}BuCHO}} \underset{Z:E\ 98.5:1.5}{\mathrm{t\text{-}BuCH{=}CHC_7H_{15}}} \tag{6.237}$$

Table 6.20. Yields and *Z*:*E* isomer ratio of olefins in hexametapol (Eq. 6.236)[639]

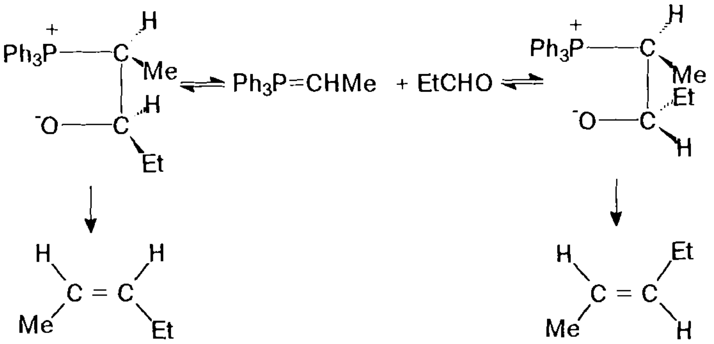
R^1	R^2	Yield (%)	Isomer proportion (%)	
			Z	*E*
Ph	Ph	84	47	53
Me	Ph	55	86	14
Et	Et	82	96	4
Pr	Pr	78	95	5

The Wittig reaction in non-polar solvents, e.g. benzene, containing dissolved lithium salts is *E*-stereoselective (Table. 6.21, Eq. 6.241)[647]:

$$[\mathrm{Ph_3\overset{+}{P}CH_2Et}]\ \mathrm{Br}^- \xrightarrow{\mathrm{NaNH_2}} \mathrm{Ph_3P{=}CHEt} \xrightarrow{\mathrm{PhCHO}} \mathrm{PhCH{=}CHEt} \tag{6.241}$$

The high *cis*-selectivity of the Wittig reaction of non-stabilized ylides in non-polar media can be explained by the low reversibility of betaine formation, which is lower than for stabilized ylides[647-649]. It should be noted that the *erythro* betaine, the direct precursor of *cis* olefin, is formed faster than the *threo* betaine (Scheme 6.117):

In the presence of lithium salts dissolved in the reaction solution the decomposition of both diastereomeric betaines to alkene proceeds slowly because of formation of the complex with the lithium cation. The *erythro* isomer is converted to the thermodynamically more stable *threo* isomer, reducing the amount of *Z* olefin. The absence of salt effects in more polar aprotic media is connected with destabilization of the betaine–cationic complex, owing to preferential solvation of the cation[652-655].



Scheme 6.117

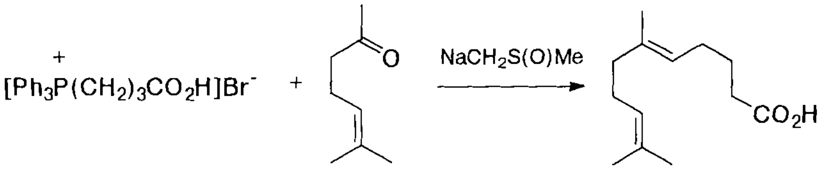
Table 6.21. Effect of additives on the $Z{:}E$ alkene ratio in benzene solution (Eq. 6.241)[647]

Additive	Yield (%)	Amount of isomer (%)	
		Z	E
Without additive	88	96	4
LiCl	80	90	10
LiBr	80	86	14
LiI	81	83	17
$LiBPh_4$	60	52	48

It is necessary to use-salt free ylide solution for the preparation of Z alkenes by the Wittig reaction in non-polar media. A variety of methods for the preparation salt-free ylide solutions is accessible from literature sources (Chapter 2).

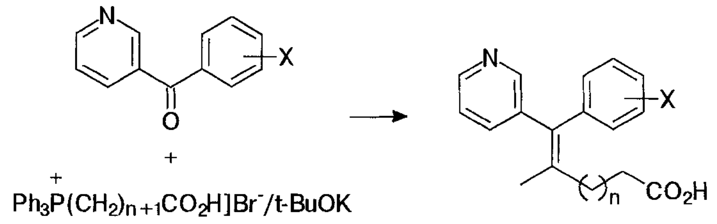
The substituents both of the ylide and of the carbonyl compound are also very important. For instance ylides with unbranched alkyl substituents R and primary aliphatic aldehydes afford alkene mixtures with a high proportion of Z isomers (90–95%). α,β-Unsaturated or aromatic aldehydes, however, react with non-stabilized ylides to furnish olefins with moderate Z alkene stereoselectivity[2,10,30,647,656].

The *cis*-selectivity of the reaction of non-stabilized ylides with unsymmetrical ketones is lower than for aldehydes. For instance, the reaction of ylide with 6-methylhept-5-ene-2-one in 1:1 THF–DMSO solution affords C_{13}-diene acid as a mixture of Z and E isomers in the ratio 3:2 (Eq. 6.242)[657]:Activated alumina efficiently promotes the Wittig reaction resulting in a high yield and high E-stereoselectivity[243].



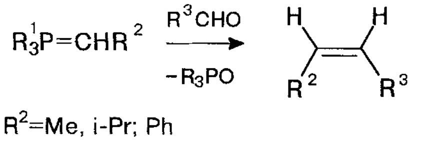
(6.242)

There are exceptions to this general stereoselectivity. For example, Maryanoff and Duhl-Emswiller[658] observed anomalous *E*-stereoselective Wittig reaction of aromatic aldehydes with (4-carboxybutylidene)triphenylphosphonium [$Ph_3P{=}CH(CH_2)_3CO_2M$, M = Li, Na, K] an ylide commonly employed in the synthesis of prostaglandins and related compounds because of its high *Z*-stereoselectivity when reacted with aliphatic aldehydes. Takeuchi and coworkers[659] reported the unusual stereoselectivity of the reaction of aromatic ketones with carboxy phosphonium ylides (Eq. 6.243). Abnormally high *E*-stereoselectivity was also observed with ketones bearing an aromatic sulfonamido group.



(6.243)

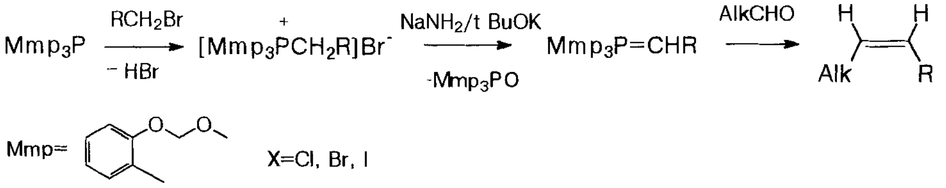
Only in rare instances are high *Z*:*E* ratios obtained with aliphatic ketones. Thus, treatment of triphenylphosphonium heptadecylmethylide with ketone in dimethylformamide–THF affords predominantly the *Z* isomer of methyl 8-methylhexacos-8-enoate (Eq. 6.244)[660]:



(6.244)

Schlosser and coworkers[54] found that ylides with an α,β-unbranched aliphatic side-chain, such as 2f, and saturated-chain aldehydes give olefins with unprecedented *cis*-selectivity (*Z*:*E* ≈ 200:1). The salt-free modification of the Wittig reaction affords the simplest access to *cis* olefins. Schlosser and coworkers[54] studied the affect on the stereoselectivity of the Wittig reaction of *ortho* substituents on the phenyl and heteroaromatic groups on the phosphorus atom of non-stabilized ylides (Table 6.22). They found that although triphenylphosphonium ethylide reacts with alkyl or arylaldehydes to afford alkenes with moderate *cis*-selectivity (84–95%), *tris*(2,6-difluorophenyl) phosphonium ethylide and *tris*(2-tolyl)phosphonium ethylide reacted with the same alkyl- and arylaldehydes to furnish *Z* olefins with 96–99% *Z*-selectivity[661]. Higher Z-selectivity was also apparent for tris(2-thienyl) and tris(2-furyl) phosphonium ylides[661].

The highest *cis*-selectivity was reported for the Wittig reaction of tris(2-methoxymethoxyphenyl)phosphonium ylides (Table 6.23)[40,661,662], which can be readily obtained from accessible starting compounds (Eq. 6.245).



(6.245)

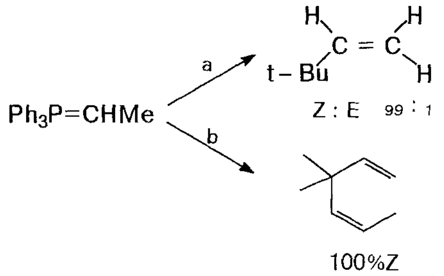
Table 6.22. Stereoselectivity of the Wittig reaction of phosphorus ylides with aldehydes (Eq. 6.244).[661]

R^3	$R^{1\ *)}$	*Z*:*E* olefin ratio	
		R^2=Me	R^2=I-Pr
$Me(CH_2)_2C=CH$	**a**	84:16	-
	c	96:4	-
	f	75.5:24.5	87,5:12,5
E-$Me(CH_2)_2CH=CH$	**a**	90:10	-
	c	96.5:3.5	-
	d	97.0:3.0	-
	f	86,5;13.5	
Ph	**a**	91.5:8.5	96.5:3.5
	b	99.0:1.0	98.5:1.5
	c	94.5:5.5	99:1.0
	f	96.5:3.5	
$Me(CH_2)_4$	**a**	95,5:4,5	98,5:1,5
	b	99,0:1,0	99,0:1
	d	99,0:1.0	98,5:1,5
	f	96.5:3,5	
c-C_6H_4	**a**	97,5:2.5	-
	f	98.5:1.5	98.5:1.5
t-Bu	**a**	99.5:1.5	99.0:1.0
	f	91.5:8.5	98.5:1.5

*) R= Ph (**a**); 2,6-$F_2C_6H_4$ (**b**), 2-MeC_6H_4 {**c**}; 2-thienyl (**d**); 2-furyl (**e**); 2-$C_6H_4OCH_2CH_2OCH_3$ (**f**)

Tris(2-methoxymethoxyphenyl) phosphonium ethylide and butylide react with saturated unbranched aliphatic aldehydes to afford olefins with very high *cis*-selectivity (99.5%). The authors[662] supposed that this type of phosphonium ylide should find widespread application.

Steric factors can be also responsible for the *Z* selectivity of the Wittig reaction of non-stabilized ylides with aldehydes. Thus, the reaction of triphenylphosphonium ethylide with such sterically hindered aldehydes as pivaldehyde or 2,2-dimethylbutene-3-al affords almost exclusively *Z* alkenes even in the presence of lithium salts (Scheme 6.118).[663]



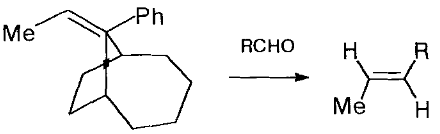
a= t-BuCHO; b= $CH_2=CHC(Me_2)CHO$

Scheme 6.118

Table 6.23. Comparison of the selectivity of triarylphosphonium ylides $(2\text{-}RC_6H_4)_3P=CHX + PhCHO \rightarrow PhCH=CHX$

R	X	*E*	*Z*
H	Cl	23	77
OCH_2OMe	Cl	2	98
H	OMe	76	24
OCH_2OMe	OMe	6	94
H	Ph	45	55
OCH_2OMe	Ph	23	77

Vedejs and coworkers found that dibenzophosphole ylides are selective reagents for the conversion of aldehydes into *E* alkenes. Alkene ratios are generally better than 90:10 *E*:*Z* and can exceed 100:1 *E*:*Z* for α-branched aldehydes, depending on the ylide substituent (Eq. 6.246).

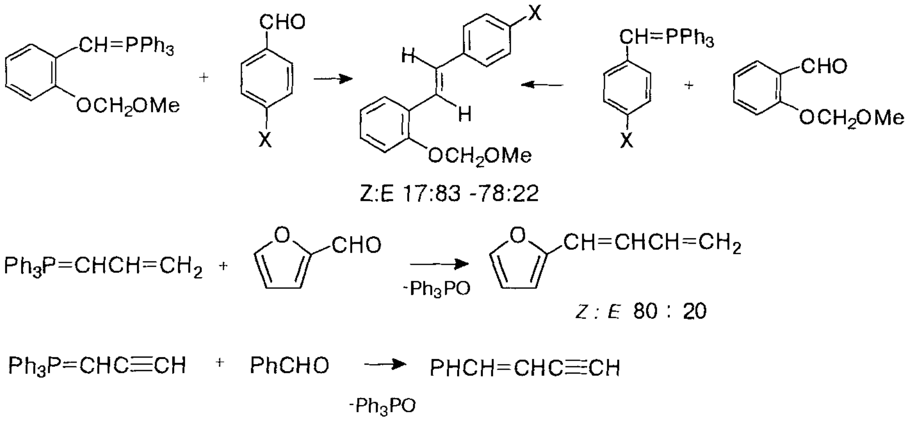


(6.246)

These ylides, however, give stable intermediate oxaphosphetanes, which must be heated to induce conversion to the alkenes. Vedejs has recently shown that phosphole-derived ethylides are extremely *E*-selective in reactions both with aldehydes and ketones[664–666]. Some conventional $Ph_3P=CHR$ ylides also provide practical access to *E* alkenes. Schlosser proposed β-oxidoylides[647], Salmond γ-oxidoylides[667], and Marryanoff carboxylic ylides[668].

6.5.1.3 Semi-stabilized Ylides

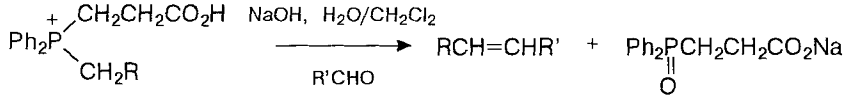
In contrast to stabilized and non-stabilized ylides, semi-stabilized ylides, or ylides of moderate activity, react with carbonyl compounds to afford mixtures of *Z* and *E* olefins (Scheme 6.119)[669–672]:



Scheme 6.119

The stereochemistry of the Wittig reaction of semi-stabilized ylides depends comparatively weakly on the nature of the solvent and on the presence of dissolved lithium salts. In non-polar solvents in the presence of the lithium halides the proportion of the *Z* olefins increases only slightly[663]. In proton-containing solvents the presence of dissolved lithium iodide increases the ratio of *E* olefins. The effect of dissolved salts and the nature of the solvent on the *Z*:*E* olefin ratio from the Wittig reaction of semistabilized ylides is shown in the Tables 6.24 and 6.25 which summarizes the effect of substituents, solvents and additives on the stereoselectivity of the Wittig reaction of semi-stabilized ylides. [673]

The stereoselectivity of the Wittig reaction of semi-stabilized ylides depends essentially on structural factors. Thus, replacement of the triphenylphosphonium group by a diphenylphosphinopropionic acid group in the Wittig reaction also increases the *E*-selectivity and provides water-soluble phosphine oxide which can be separated. The best result were obtained under phase-transfer conditions (Eq. 6.247)[674]:



$$\overset{+}{Ph_2P}(CH_2CH_2CO_2H)(CH_2R) \xrightarrow[R'CHO]{NaOH,\ H_2O/CH_2Cl_2} RCH{=}CHR' + Ph_2\overset{\displaystyle O}{\overset{\|}{P}}CH_2CH_2CO_2Na \qquad (6.247)$$

E:*Z*=91:9

R=Ph, 4-O2NC6H4, CN, CO2Me; R'=i-Pr, Ph

The stereoselectivity of the Wittig reaction is greater for sterically hindered semi-stabilized ylides. The replacement of phenyl groups on butyl group at the phosphorus atom of allylphosphonic ylides favors the formation of *E* olefins in the sequence:

$RR'CH{=}CRCH{=}PBu_3 > CH_2{=}CRCH{=}PBu_3 > RR'C{=}CHCH{=}PBu_3 > RCH{=}CHCH{=}PBu_3 >$
$RCH{=}CHCH{=}PPh_3$. [676,677]

Table 6.24. The stereochemistry of the Wittig reaction of semi-stabilized ylides

R(RCHO)	Solvent	Salt effect	Stereoselctivity
Alk, Ar	Non-polar	Dependent	*E* > *Z*
Et, Ph	Non-polar	Dependent	*Z*
Pr	Non-polar	Not dependent	*E* > *Z*
Alk, Ar	Polar, aprotic	Not dependent	*E* + *Z*
			E + *Z*
Ph	Polar	Dependent	LiI, NaI increase the amount of *E* isomer, LiCl has no effect

$$\mathrm{Ar_3P{=}CHPh} + \mathrm{RCHO} \longrightarrow \mathrm{RCH{=}CHPh} + \mathrm{Ar_3PO} \qquad (6.248)$$

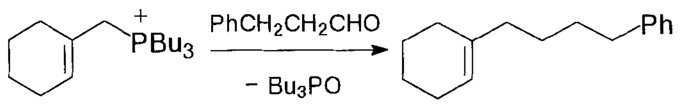
$\mathrm{Ar{=}Ph,\ 4\text{-}MeC_6H_4,\ 2\text{-}MeC_6H_4;\ R{=}Me,\ Ph}$

Table 6.25. Effect of the reaction conditions on the stereoselectivity of the reaction of $Ph_3P{=}CHPh$ with benzaldehyde (Eq. 6.248)

Base	Solvent	*Z*:*E*	Ref.
PhLi	Ether	3:7	319a
NaOEt	Ethanol	53–66:47–34	205,679
NaOEt	DMFA	74:26	319a
NaOEt + LiBr	DMFA	81:19	319a
BuLi + LiBr	DMFA	62:38	641
BuLi	benzene	34:66	641
BuLi + LiBr	benzene	1:1	641
t-BuOK	*tert*-butanol	1:3	682
NaOH	$CH_2Cl_2 + H_2O$	59:41	205
$NaNH_2$	benzene	44:56	647

The *Z*:*E* ratio of alkenes prepared by Wittig reaction of benzaldehyde, acetaldehyde, or pivaldehyde with semistabilized ylides, derivatives of benzyltriarylphosphonium salts deprotonated with an ethanol solution of sodium ethylate, increases when the steric hindrance at the phosphorus atom is increased (Table 6.26, Eq. 6.249, 250)[53]:

$$\mathrm{R_3P{=}CHPh} + \mathrm{ArCHO} \longrightarrow \mathrm{ArCH{=}CHPh} + \mathrm{Ar_3PO} \qquad (6.249)$$



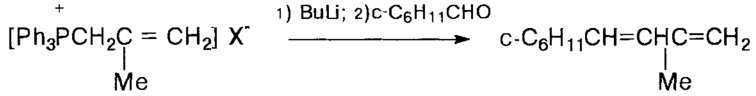
(6.250)

n=1, E:Z=94:6; n=2, E:Z=96:5

Increase the volume of the substituents R in RCHO reacting with triphenylphosphonium allylides leads to an increase in *Z* selectivity in the sequence *t*-Bu > Ph > $PhCH_2CH_2$ > $c\text{-}C_6H_{11}$ (Eq. 6.251–6.253): Evidently, variation of the substituents of semi-stabilized ylides and aldehydes enables direction of the reaction toward the preferential formation of the *Z* or *E* olefin (Table 6.27).

$$[\mathrm{Bu_3\overset{+}{P}CH_2CH{=}CHPh}]\,\mathrm{X^-} \xrightarrow{\mathrm{1)\ PhLi;\ 2)\ PhCHO}} \mathrm{PhCH{=}CHCH{=}CHPh} \quad E:Z\ 52{:}48 \tag{6.251}$$

$$[\mathrm{Bu_3\overset{+}{P}CH_2CH{=}CMe_2}]\,\mathrm{X^-} \xrightarrow{\mathrm{1)\ BuLi;\ 2)\ t\text{-}BuCHO}} \mathrm{t\text{-}BuCH{=}CHCH{=}CHPh} \quad E:Z\ 5{:}95 \tag{6.252}$$



$$[\mathrm{Ph_3\overset{+}{P}CH_2\underset{Me}{C}{=}CH_2}]\,\mathrm{X^-} \xrightarrow{\mathrm{1)\ BuLi;\ 2)c\text{-}C_6H_{11}CHO}} \mathrm{c\text{-}C_6H_{11}CH{=}CH\underset{Me}{C}{=}CH_2} \tag{6.253}$$

Table 6.26. Effect of phosphorus and aldehyde substituents on the selectivity of the Wittig reaction (Eq. 6.249):

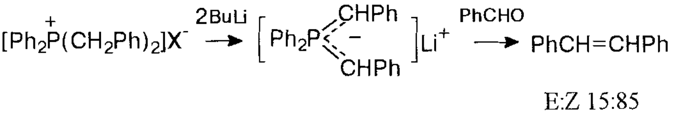
R_3P	Ar	Base	Solvent	*Z*:*E*	Ref.
Ph_3P	Ph	NaOEt	EtOH	53:47	679
Ph_2MeP	Ph	NaOEt	EtOH	28:72	680
$PhMe_2P$	Ph	NaOEt	EtOH	13:87	680
$(c\text{-}C_6H_{11})_3P$	Ph	NaOEt	EtOH	5:95	630
PhEtMeP	Ph	PhLi	Et_2O	5:95	131
Ph_3P	$4\text{-}MeC_6H_4$	NaOH	$CH_2Cl_2\text{–}H_2O$	44:56	205
Ph_3P	$4\text{-}MeC_6H_4$	$NaNH_2$	C_6H_6	36:64	647
Ph_3P	$4\text{-}ClC_6H_4$	$NaNH_2$	C_6H_6	10:90	647
Ph_3P	$4\text{-}NO_2C_6H_4$	NaOH	$CH_2Cl_2\text{–}H_2O$	56:44	205

Table 6.27. Wittig reactions of $Ph_2(Me)P{=}CHPh$ with PhCHO and *t*-BuCHO in THF at –78°C in the presence of metal iodides

Aldehyde	Base used	Yield of alkene(%)	*cis*:*trans*
Benzaldehyde	BuLi	91	63:37
Benzaldehyde	NaHMDS	96	69:31
Benzaldehyde	KHMDS	84	19:81
Pivaldehyde	BuLi	95	63:37
Pivaldehyde	NaHMDS	88	69:31
Pivaldehyde	KHMDS	95	21:79

McEwen and Ward found that in the reaction between triphenylphosphonium benzylide and benzaldehyde the product mixture is enriched with the *Z* alkene when the lithium anion is present whereas the *E* isomer predominates when sodium or potassium ions are present (Table 6.28)[683].

McKenna and Valker reported that ylide anions prepared from benzylphosphonium salts react with 1 or 2 equiv. of benzaldehyde to furnish *E*-stilbene in high yield (Eq. 6.255)[678,684]:



$$[Ph_2\overset{+}{P}(CH_2Ph)_2]X^- \xrightarrow{2BuLi} \left[Ph_2P\begin{matrix}CHPh\\ -\\ CHPh\end{matrix}\right]Li^+ \xrightarrow{PhCHO} PhCH{=}CHPh \qquad (6.255)$$

E:Z 15:85

Ylides with a dibenzophosphole ring on the phosphorus react with aldehydes affording very high *E*-stereoselectivity. The *E*-Stereoselectivity of dibenzophosphole ylides is 6:1 for benzaldehyde and >100:1 for tertiary alkylaldehydes[685].

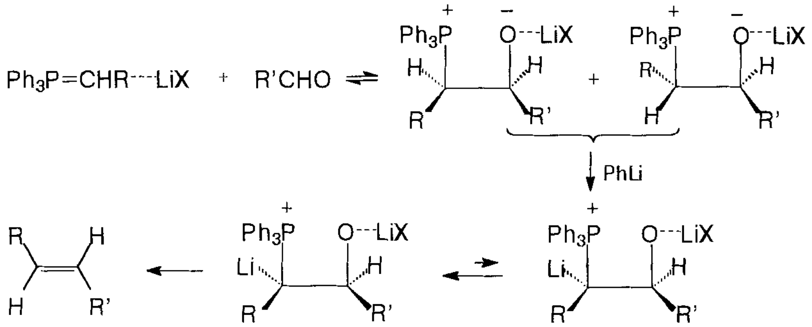
The effect of *β*-cyclodextrin on the *Z*:*E* selectivity of the Wittig reaction with semistabilized ylides has been described[173].

Yamataka and coworkers[737] reported that the *cis*:*trans* ratio of the stilbene formed by reaction of benzaldehyde with triphenylphosphonium benzylide was essentially unchanged by changing the concentration, the mode of addition, and the molar ratio of aldehyde to ylide. The results could be rationalized by assuming a chelating interaction between the lone pair of the *ortho* substituents and the phosphorus of the ylide

6.5.2 The Wittig–Schlosser Reaction

The creation of conditions which accelerate the equilibrium between the *threo* and *erythro* betaine diastereoisomers, precursors of *cis* and *trans* olefins, enables the *E*-stereoselectivity of the Wittig reaction to be increased. Schlosser described a method leading to olefins in very high *E*-selectivity, even with non-stabilized ylides[647,687]. Treatment of the initially formed betaine–lithium complex with an organolithium reagent affords a new *β*-oxido-phosphorus ylide. Whereas the initially formed *erythro* betaine is stable to inversion, its lithium derivative, a *β*-oxide ylide, is readily interconverted even at low temperature. The inversion of *β*-oxidoylides proceeds rapidly at the carbon atom to result in the predominant formation of the thermodynamically more stable *threo* isomer. Addition of acid to the reaction medium regenerates the starting betaine of predominantly *threo* configuration. Elimination of phosphine oxide from this *threo* betaine results in almost stereochemically pure *E* olefin (Scheme 6.120)[687–689].

This reaction proceeds stereoselectively with unsymmetrical ketones also. For instance, reaction of triphenylphosphonium ethylide with acetophenone affords *E*- and *Z*-phenybut-2-ene in 89:11 ratio whereas the traditional Wittig reaction furnishes alkenes in the ratio 40:60.

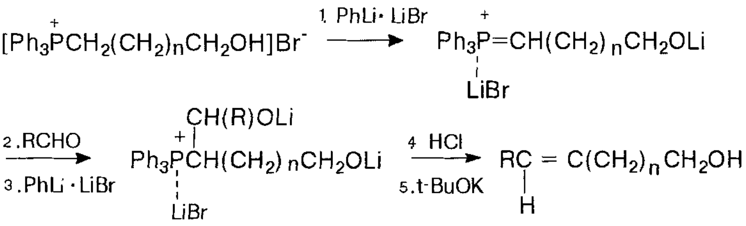


Scheme 6.120

The reaction can be performed with polymer-supported ylides. Thus, treatment of phosphonium salts supported on polystyrene with butyllithium in THF and subsequent reaction of the prepared ylide with acetophenone, and then with butyllithium, affords β-oxidoylides which after neutralization with acid and treatment with the potassium *tert*-butoxide afford predominantly *E* alkene. Under ordinary conditions the reaction of salt-free ylides with acetophenone affords almost pure *Z* olefin[690].

This Schlosser modification of the Wittig reaction, now known as the 'Wittig–Schlosser reaction', provides good yields of *E* alkenes from a variety of aliphatic and aromatic aldehydes, and non-symmetrical ketones.

The Wittig–Schlosser reaction was used for the synthesis of alkenol-type pheromones[690]. Generating of ylides from ω-hydroxyalkyltriphenylphosphonium bromides with different numbers of methylene groups in the side-chain enabled the preparation of alkenols with high *trans*-selectivity—the stereochemical purity of the alkenols was 97–99%. Schlosser also developed one-pot method for the synthesis of alkenol pheromones (Scheme 6.121)[691]:



$$[Ph_3\overset{+}{P}CH_2(CH_2)_nCH_2OH]Br^- \xrightarrow{1.\ PhLi\cdot LiBr} \underset{LiBr}{Ph_3\overset{+}{P}}=CH(CH_2)_nCH_2OLi$$

$$\xrightarrow[3.\ PhLi\cdot LiBr]{2.\ RCHO} \underset{LiBr}{Ph_3\overset{+}{P}}\overset{CH(R)OLi}{C}H(CH_2)_nCH_2OLi \xrightarrow[5.\ t\text{-}BuOK]{4\ HCl} R\underset{H}{C}=C(CH_2)_nCH_2OH$$

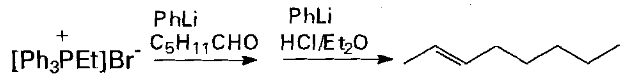
Scheme 6.121

One-pot synthesis of dodecene-5-ol (Scheme 6.121).[691]

A solution of 4-hydroxybutyltriphenylphosphonium bromide (8.3 g, 20 mmol) in THF (60 mL) was added dropwise to a solution of phenyllithium (40 mmol) in 5:3 THF–ether (40 mL) to give a red solution. The reaction mixture was stirred for 20 min at 25°C and cooled to –75°C. Hexanal (2 g, 20 mmol) was then added and the reaction mixture was stirred at –30°C for 20 min. Phenyllithium (40 mmol) in 5:3 THF–ether (40 mL) was again added, resulting in the formation of a slightly colored precipitate. This dark-red betaine–ylide solution was left for 30 min at 25°C and then the solution was cooled to –75° C. and a solution of potassium *tert*-butoxide (5.0 g, 45 mmol, 10 mL) was added and the reaction mixture was stirred for 1h at 25°C. The reaction mixture was diluted with water (25 mL) and extracted with diethyl ether (2 x 25 mL). The extracts were dried, evaporated, and the residue was treated with pentane to separate the triphenylphosphine oxide. The solvent was removed under reduced pressure and the residue was distilled under vacuum to give 2.45 g (78%) of *E*-dodecen-5-ol, bp 111–113°C (13 mm Hg), n_D^{20} 1.4529. *Z*:*E* olefin ratio is 2:98.

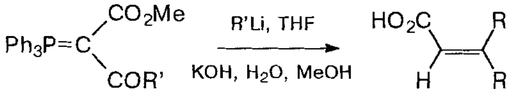
E-oct-2-ene (Eq. 6.256)[650]

A solution of phenyllithium (15 mL, 2.0 M) in cyclohexane–ether was added to a suspension of ethyltriphenylphosphonium bromide (11.1 g, 30 mmol) in dry ether (30 mL) in a round-bottomed flask closed with a rubber septum and an outlet to a nitrogen line. The mixture was stirred for 10 min at –70°C in a dry-ice–acetone cooling bath and a solution of hexane (3 g, 30 mmol) in absolute ether (10 mL) was added dropwise with stirring. The temperature of the reaction mixture was increased to –30°C and a solution of phenyllithium (30 mmol) in ether was added dropwise with stirring. The mixture was then stirred for 2 h at +20°C and filtered or centrifuged. The mixture was washed with water, dried with $MgSO_4$, and evaporated under reduced pressure. The residue was purified by distillation, bp 121°C (740 mmHg) to give the desired product. Yield 70%, *E*:*Z* = 99:1



(6.256)

Shen and Wang[692] proposed a method similar to the Wittig–Schlosser reaction for the synthesis of unsaturated carboxylic acids (Table 6.28, Eq. 6.257):

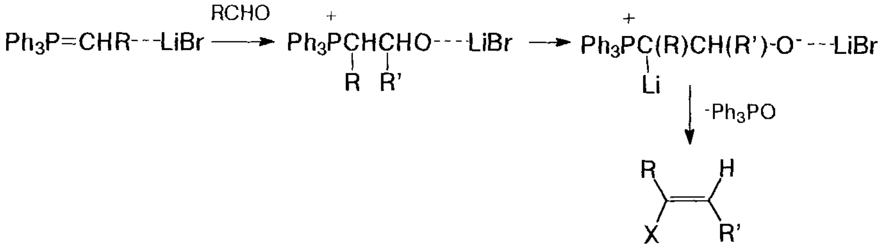


(6.257)

Table 6.28. Synthesis of unsaturated carboxylic acid (Eq. 6.257)[692]

R^1	R^2	Yield (%)	*Z*:*E*
CF_3	Bu	92	15:85
C_2F_5	Bu	94	9:91
C_3F_7	Ph	90	38:62

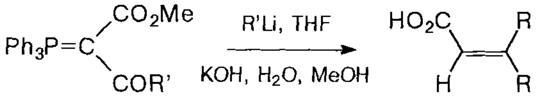
Betaine ylides which are easily accessible through α-deprotonation of P-betaines react with a wide spectrum of electrophilic reagents to yield α-substituted P-salts. Treatment with deuterium, alkyl, or halogen donors produces α-deutero-, α-alkyl-, or α-halogen-substituted betaines (Scheme 6.122)[698b]. These decompose spontaneously to triphenylphosphine oxide and olefins substituted at a vinyl position



Scheme 6.122

6.5.3 Substitution and Carbonyl Olefination via β-Oxidophosphonium Ylides (The SCOOPY Method)

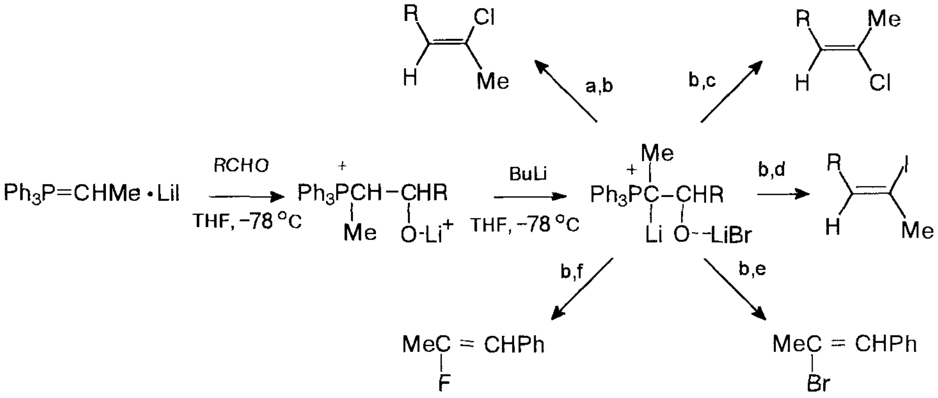
Another useful extension of the classic Wittig reaction is the SCOOPY method of olefination or '*α*-substitution plus carbonyl olefination via *β*-oxido phosphonium ylides' *β*-Oxidoylides react readily with various electrophiles to form *α*-substituted betaines which decompose to triphenylphosphine oxide and substituted alkene. The elimination of the phosphine oxide from those *α*-substituted betaines proceeds spontaneously under heating or after treatment with potassium *tert*-butoxide. The reaction is highly stereoselective and results in the formation of substituted *E* alkenes (Eq. 6.258)[689,696,697]:



(6.258)

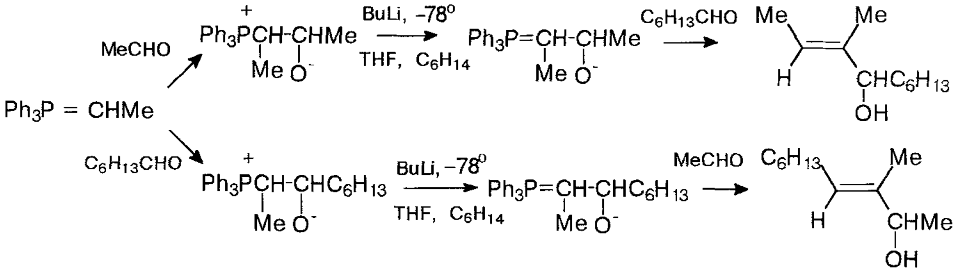
Abell and coworkers[694] proposed halogenation of keto acid ylides by the SCOOPY method. The treatment of the *β*-oxidoylide with *N*-chlorosuccinimide followed by elimination of phosphine oxide gave the *E* isomer of 2-chloro-non-2-ene, whereas treatment of the *β*-oxidoylide with iodobenzene dichloride resulted in predominantly the *Z* alkene. Iodoalkenes can be obtained by treatment of the *β*-oxidoylides with mercuric acetate and then with anhydrous lithium iodide and iodine. *β*-Oxidoylides react with bromine to furnish bromoalkenes with large amounts of the *E* isomer. Fluorination of *β*-oxidoylides with perchloryl fluoride affords fluoroalkenes (Scheme 6.123).

The most interesting SCOOPY application of *β*-oxidoylides is their reaction with aldehydes, leading to the formation of allylic alcohols. This reaction is highly stereo- and regioselective. For instance, reaction of the triphenylphosphonium ethylide with acetaldehyde, and then, after the treatment with alkyllithium and the formation of the *β*-oxidoylide, with heptanal results in the alcohol alone. When the aldehydes are added in the reverse order the isomeric alcohol was obtained exclusively (Scheme 6.124)[699]. This reaction is versatile tool for the preparation of allyl alcohols of various structures with very good stereo- and regioselectivity.



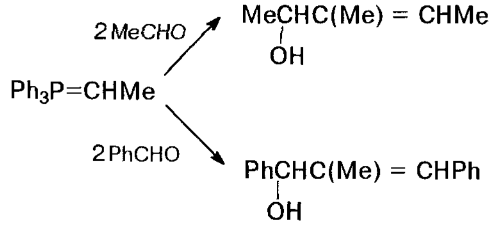
R = C_6H_{13}; *a* = *N*-chlorosuccinimide; *b* = *t*-BuOK; *c* = $PhICl_2$; *d* = $Hg(OAc)_2$ + I_2 or LiI; *e* = Br_2; *f* = $FClO_3$

Scheme 6.123



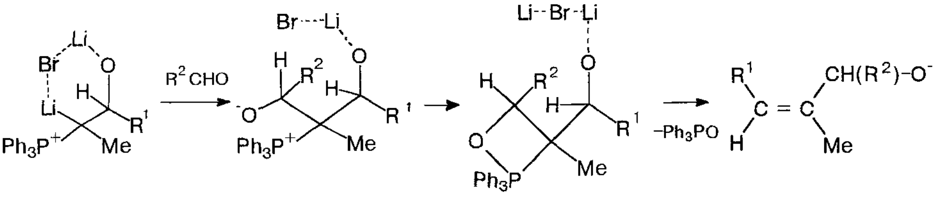
Scheme 6.124

Corey[700] proposed a *β*-oxidoylide route to olefins enabling the joining of the carbons of three components in such away that the oxygen of the first aldehyde component is retained whereas that of the second aldehyde is eliminated as phosphine oxide. This positional specificity for the olefin synthesis could be demonstrated for benzaldehyde. For instance, reaction of triphenylphosphonium ethylide with two equivalents of acetaldehyde results in 3-methylpent-2-ene-1-ol in 65% yield and an *E*:*Z* isomer ratio of 93:7. Both carbonyl components can be aromatic aldehydes. The reaction of triphenylphosphonium ethylide with 2 equiv. benzaldehyde affords the *E* isomer only of 1,3-diphenyl-2-methylprop-2-ene-1-ol (Scheme 6.125)[700]:



Scheme 6.125

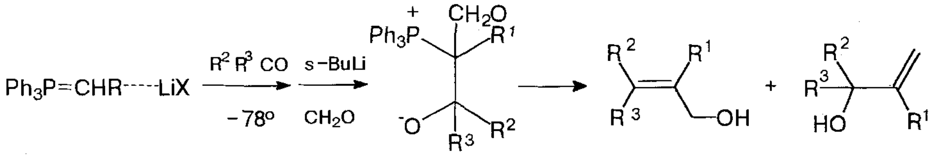
The reaction resulted in the allylic alcohol formed by elimination of oxygen from the second aldehyde. The high stereo- and regioselectivity of the reaction of β-oxidoylides with carbonyl compounds can be explained by the formation of cyclic complexes with lithium halides proceeding with high diastereoselectivity (Scheme 6.126)[699]:



Scheme 6.126

The reaction of the cyclic complex with the aldehyde proceeds under the conditions of minimum steric interaction and subsequent reaction with the second molecule of carbonyl compound results in a betaine with two negatively charged oxygen atoms, one of which is connected to the lithium halide. The formation of the oxaphosphetane intermediate thus proceeds with the participation of the oxygen atom of the second carbonyl compound, which is then removed with triphenylphosphine oxide. The stereochemistry of the alkene formed by reaction of aldehydes with oxidoylides depends dramatically on the distance between the oxygen and phosphorus atoms: the production of *E* alkenes is favored by ylides with proximal oxygen and phosphorus atoms[695].

The stereoselectivity of the reaction also depends on the temperature. Thus, −78°C the reaction of the β-oxidoylide prepared from heptanal and triphenylphosphonium ethylide, with heptanal as the second carbonyl component affords a mixture of alcohols **25, 26** in 9:1 ratio. At 0–20°C the isomer ratio was only 3:1[699]. The reaction of β-oxidoylide with paraformaldehyde as the second carbonyl component, in contrast with other aldehydes, affords the allylic alcohol formed by loss of oxygen from the first carbonyl compound (Eq. 6.259)[701]:



25 **26**

(6.259)

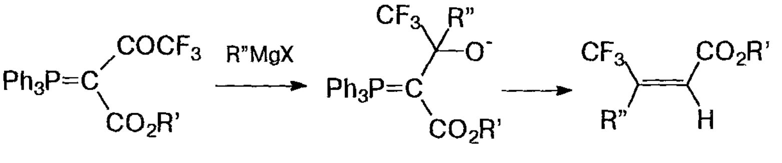
If the first carbonyl component is a sterically hindered aldehyde or a ketone the oxygen atoms are lost from both carbonyl reagents, resulting in a mixture of isomeric allylic alcohols. With acetone as a first carbonyl compound the elimination of oxygen proceeds from the formaldehyde to form only primary allylic alcohol (Table 6.29).

The selectivity of the reaction of β-oxidoylides with paraformaldehyde as one of the aldehyde components depends on the order of addition of the aldehydes[704].

Table 6.29. Yields and stereochemistry of the formation of allylic alcohols (Eq. 6.259)[701]

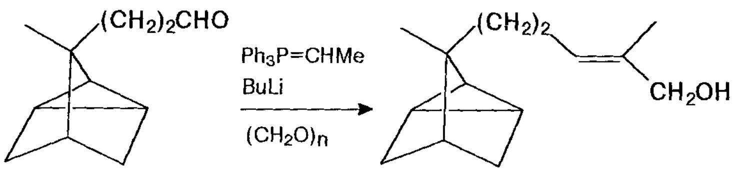
R^1	R^2	R^3	Yield of **25** (%)	*E*:*Z*	Yield of **26** (%)
Me	Ph	H	28	99:1	12
Me	C_5H_{11}	H	71	99:1	0
Me	C_6H_{13}	H	76	99:1	0
H	$-(CH_2)_4-$		37	–	10
H	Me	Me	0	–	41
Me	Me	H	–	–	–
H	Ph	H	31	1:99	10

Thus, triphenylphosphonium ethylide reacts with hexanal and then with paraformaldehyde to afford a *Z*:*E* isomer mixtures of alcohols, $R^1 = R^3 = H$, $R^2 = C_5H_{11}$ (in 36:64 ratio). Conversely, the reaction of triphenylphosphonium methylide with paraformaldehyde and then with hexanal affords only the *Z* isomer of the alcohol. Fluorinated dicarboxyylides reacted with a variety of Grignard reagents to give β-oxidoylides[702]. Treatment of the β-oxidoylides with acetic acid or saturated aqueous methylamine hydrochloride followed by elimination of Ph_3PO gave trifluoromethylated α,β-unsaturated esters with the *Z* isomers being the major products (Eq. 6.260):

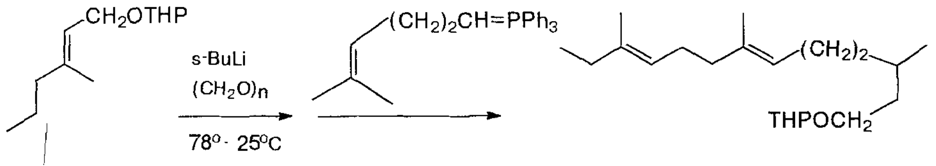


(260)

An indirect Wittig reaction via isolation of a 1,2-hydroxyphosphonium salts and subsequent treatment with a base shows identical stereoselectivity with the corresponding direct Wittig reaction.[686] The SCOOPY method is an important synthetic tool in the synthesis of naturally occurring compounds[693]. Thus, the significance of this method (proposed by Schlosser) for the stereo-controlled synthesis of allylic alcohols was demonstrated by Corey using α-santalole as an example (Eq. 6.261).[99] Another example of such a synthesis is the preparation of key compound in the total synthesis of juvenile hormone (Eq. 6.262):

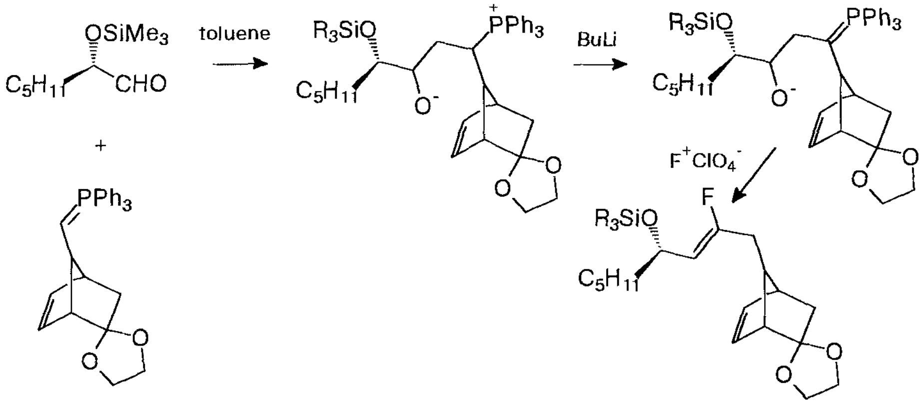


(6.261)



(6.262)

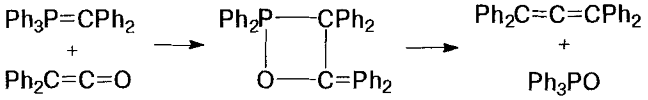
β-Oxidoylides have been used in the synthesis of prostaglandins[450] and fluoroprostaglandins[703]. The total synthesis of fluoroprostaglandin $F_2\alpha$ methyl ester was developed starting from the readily available bromoketoester[703]. Construction of the β-fluoroolefinic structural unit was achieved via a Wittig–Schlosser reaction employing a chiral aldehyde and a chiral ylide. (+)-13-Fluoroprostaglandin $F_2\alpha$ methyl ester was evaluated for interruption of pregnancy in the hamster and its smooth-muscle-stimulating properties on hamster uterine strips (Scheme 6.127)



Scheme 6.127

6.6. The Mechanism of the Wittig Reaction

The mechanism of the Wittig Reaction has been a subject of intensive investigations from its discovery. The first attempt to explain the mechanism of the reaction was reported many years before Wittig discovery. In 1919 Staudinger and Meier have considered a four center process via $1,2\lambda^5$-oxaphosphetane intermediate formation although it was not intended as a mechanistic suggestion in the current context (Eq. 6.263).[1]



(6.263)

The mechanism of the Wittig Reaction has been reviewed many times. The most recent reviews were published by Vedejs[12,623] in 1994 and 1996 and Maryanoff and Reits in 1989[705]. In this chapter we give only brief historical evaluation and modern interpretation of the mechanism of the Wittig Reaction. More detailed information the reader can find certainly in the special literature.

6.6.1 Development of the Wittig Reaction Mechanism

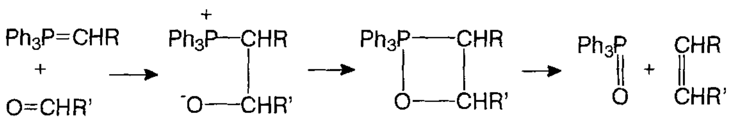
Two general types of mechanism for the Wittig reaction can, in principle, be envisaged:

a) a stepwise ionic mechanism; and

b) a direct cycloaddition mechanism.

The ionic stepwise mechanism first proposed by Wittig himself suggested a betaine as a possible intermediate in the reaction; this would subsequently undergo ring closure to give the four-membered oxaphosphetane ring which would then undergo *syn*-elimination to give the products[679].

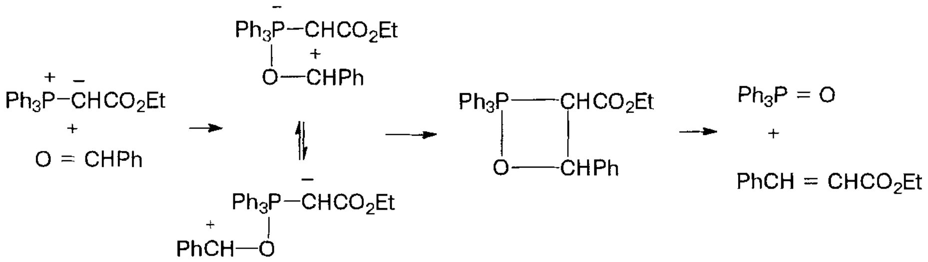
Early proposals of the mechanism of the Wittig reaction[706] proposed by Schlosser and Christmann[647], Speziale[707], Johnson[708], and Bergelson[709,710] also suggested the initial step of the reaction involved reversible addition generating a betaine intermediate. Subsequent decomposition to the alkene was believed to involve a oxaphosphetane, which was considered as a intermediate of higher energy or as four-membered cyclic transition state leading from the betaine to the alkene, via intramolecular nucleophilic attack of the negatively charged oxygen atom on the phosphonium cation. The first four-membered cyclic intermediate in the reaction of P-ylides with carbonyl compounds was reported by Staudinger[1]. Later the oxaphosphetanes as a intermediary products in the Wittig reaction were proposed by Birrum and Matthews and by Ramirez, who had succeeded in preparing the first stable representatives of these compounds (Eq. 6.263)[711-713]:



(6.264)

Bergelson and Shemyakin proposed that the mechanism of the initial step was nucleophilic attack of the carbonyl oxygen on the phosphorus atom of the ylide with the formation of an appropriate betaine (Scheme 6.128)[641,709,710]:

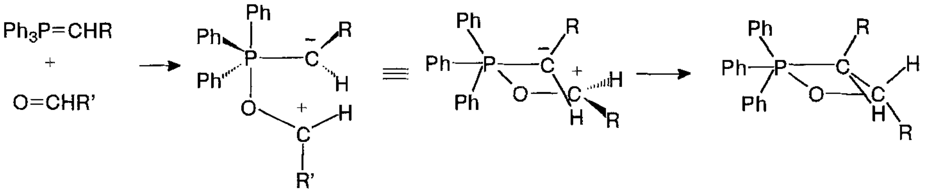
On the basis of kinetic studies they proposed a four-center process, via initial P–O interaction, as an alternative ionic pathway for the reaction of non-stabilized ylides with aldehydes. It was found that reaction of triphenylphosphonium carbonyl-stabilized ylides with aromatic aldehydes follows an approximately second order kinetic equation (first order in ylide and aldehyde). The first step of the reaction is reversible and rate-determining. Confirmation of this concept relied on the direct dependence of reaction rate on the nucleophilicity of the ylide.



Scheme 6.128

A considerable negative entropy of activation was observed ($\Delta S^{\neq} = -40$ eu) and a significance of $\rho = -2.8$ was interpreted as the consecutive formation of betaine and oxaphosphetane and then decomposition into olefin and phosphine oxide. Bergelson and coworkers proposed a hypothesis in which the formation of the betaine is the step determining the stereoselectivity of the reaction. According to Bergelson different approaches of the reactants could generate both *erythro* (*Z*-generator) and *threo* (*E*-generator) stereoisomers. Evaluation of the relative stabilities of these two isomers led to the conclusion that the *erythro* isomer is more stable and that it would be formed at the faster rate.

In 1969 Schneider studied the dependence of the stereochemistry of the reaction of non-stabilized ylides with aldehydes on the nature of the alkyl groups and observed that a considerable increase in *cis*-stereoselectivity resulted from increasing the effective volume of the substituent connected to the carbonyl group. He recognized that a perpendicular arrangement of the C=O and P=C groups could be used to explain the predominant formation of *cis* oxaphosphetane. His mechanism is in principle similar to that of Bergelson. Schneider's mechanistic chemistry was, however, the first to provide a steric basis for the *cis*-selectivity of the Wittig reaction. Schneider supposed that the first step of the Wittig reaction was the nucleophilic addition of the carbonyl oxygen to the phosphonium cation resulting in the formation of a betaine-like addition product with trigonal bipyramidal structure (Eq. 6.265)[715,716]:



(6.265)

It should be noted that Schneider's concept was not confirmed as rigorously by experiment as was the preceding mechanism proposed by Bergelson and Shemyakin.Froyen[717] reported that the mechanism of the reaction of triphenylphosphonium fluorenylide with *p*-nitrobenzaldehyde included the reversible rate-determining step of oxaphosphetane formation without the direct formation of a betaine. An analogous conclusion was also reported by Aksnes[718,719] and Ruchardt[720] who studied in detail the effect of solvents on the kinetics and on the activation parameters of the reaction of triphenylphosphonium benzoylmethylide with *p*-nitrobenzaldehyde. They came to the conclusion, that the rate-determining step was the formation of a low-polarity cyclic transition state. The measured *r* value of 1.1 is in accordance with a transition state of low polarity.

Oxaphosphetanes were recognized as probable intermediates in the Wittig reaction because *syn* elimination of the phosphine oxide from an oxaphosphetane would generate the desired alkene[10]. This hypothesis was confirmed by the use of ylides derived from an optically active phosphonium salt, which had been shown to undergo the Wittig reaction with retention of configuration at the phosphorus atom, an event which provided evidence against possible *anti*-elimination[131]. Further evidence was provided found by the isolation and characterization of unusually stable oxaphosphetanes that could be induced to give Wittig products under more drastic conditions[711,712,721]. Later it was confirmed by ^{31}P NMR spectroscopy that the oxaphosphetanes were indeed formed as intermediates in the Wittig reaction of unstabilized ylides[722].

In 1973 Vedejs and Snoble [722] discovered by means of low-temperature ^{31}P and ^{1}H NMR that the Wittig reaction of non-stabilized P-ylides proceeds with the formation of oxaphosphetane intermediates. As the temperature was increased to –15 and 0°C the oxaphosphetanes were transformed into olefins and phosphine oxides. Oxaphosphetanes stabilized by electron-withdrawing CF_3 groups have been isolated and studied by X-ray crystallography. These oxaphosphetanes contain a pentacoordinate phosphorus atom in the center of bipyramid with apical oxygen and an equatorial carbon atom previously belonging to the P=C group[721,723–725].

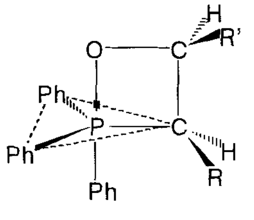


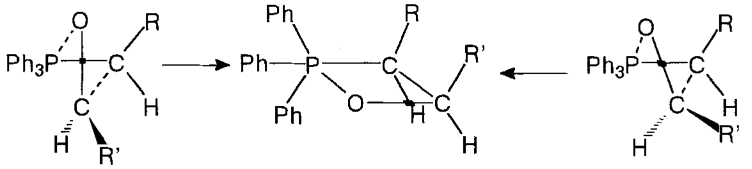
Figure 6.1

The detection of oxaphosphetanes as intermediates of the Wittig reaction could not, nevertheless, explain the *Z*-stereoselectivity of the reactions of unstabilized ylides—it would, in fact, be expected on the basis of steric considerations that *E*-oxaphosphetanes would be formed more quickly, and would be more stable, than their *Z* counterparts, and so the outcome of the reaction would be mainly formation of the *E* alkene. Although it was necessary to invoke the formation of oxaphosphetanes as intermediates to explain the products observed, it is clear that an unambiguous explanation of the unusual stereoselectivity observed was still lacking.

Betaines have not been observed spectroscopically as transient intermediates in salt-free Wittig reactions and their involvement in the Wittig reaction has also been questioned by the use of theoretical methods[726,727].

Other ionic intermediates, involving prior P–O bond formation, have been proposed by Schneider[716] and by Bestmann[728] to account for the unusual Z-stereoselectivity; the former used steric reasoning to justify the stereoselectivity observed.

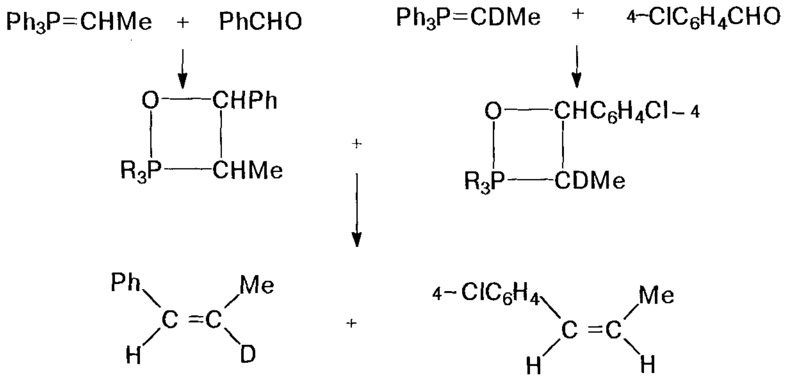
Another general mechanism invoked to rationalize the puzzling Z-stereoselectivity of the salt-free Wittig reaction of unstabilized ylides was based on the assumption of a one-step direct cycloaddition of the ylide to an aldehyde to form the oxaphosphetane. To explain the stereoselectivity Vedejs initially regarded the reaction as a synchronous symmetry-controlled $\pi 2_a + \pi 2_s$ cycloaddition process[722]. A crisscrossed approach of the reactant was necessary for proper orbital overlap. In the first variant of the Vedejs mechanism the initial step of the reaction was synchronous $[2_a + 2_s]$-cycloaddition of the ylide to the carbonyl group, leading immediately to an oxaphosphetane of *cis* configuration without need for a zwitterionic precursor and without violation of orbital symmetry rules. This type of transformation can occur if it is assumed that the crossover mode of approach of the reagents proceeds according to Woodward–Hoffman rules and results in the minimum steric disadvantageous repulsion of substituents R and R′. *syn* Elimination is the second and the definitive step of the reaction and results in an olefin of *cis* configuration (Eq. 6.266)[722]:



(6.266)

Vedejs later modified this hypothesis. He advocated the same crisscrossed geometry, but gave steric reasons for the stereoselectivity of the reaction[729]. Vedejs subsequently came to the conclusion that the lithium-free Wittig reaction is an asynchronous cycloaddition of the P=C and C=O bonds[730,731]. Non-stabilized ylides react with aldehydes via a puckered four-center geometry to give *cis*-disubstituted oxaphosphetanes, the decomposition of which occurs with retention of stereochemistry. More recently Vedejs has modified this view again, invoking an asynchronous cycloaddition with a four-center puckered transition state in which steric arguments and the hybridization states of the phosphorus atom are responsible for the Z stereoselectivity[730,731,732].

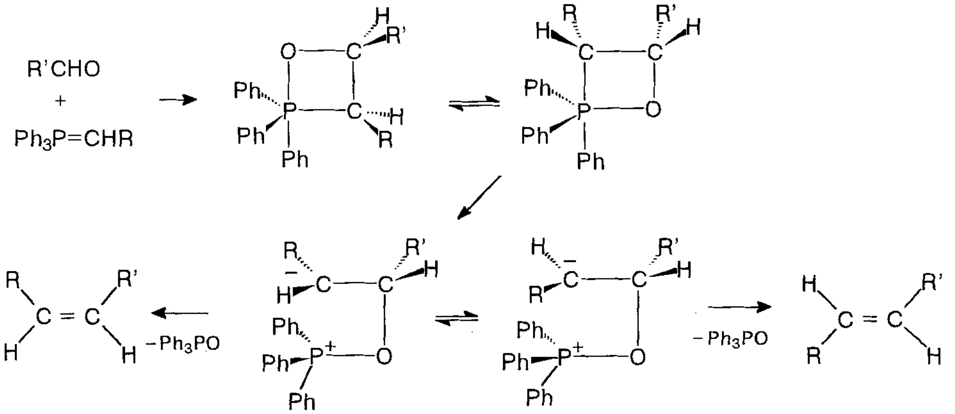
Vedejs[729] obtained interesting results from an experiment designed to investigate the possibility of crossover (Scheme 6.129) in the preparation of oxaphosphetanes by reaction of an ylide with benzaldehyde and of a deuterated ylide with *para*-chlorobenzaldehyde. One of the products isolated from the reaction mixture was β-methylstyrene of high Z-purity (93%) containing 34% deuterium. This result is evidence of the reversibility of the first step of the Wittig reaction[729].



Scheme 6.129

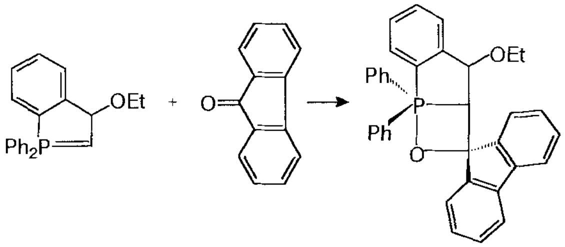
Because attempts to detect the betaine intermediate in the Wittig reaction in which the oxygen atom was not coordinated with the metal were unsuccessful, Vedejs supposed that betaines are not formed as intermediates in the Wittig reaction of non-stabilized ylides.

Bestmann[728,529] proposed that the reaction of and ylide with an aldehyde leads to the formation of an *erythro* oxaphosphetane with the oxygen in the apical position, because of the tendency of electron-acceptor atoms to occupy this position. The oxygen and carbon atoms undergo pseudorotation around the pentacoordinate phosphorus to give a new oxaphosphetane, containing an apical P–C bond and an equatorial P–O bond. Cleavage of the P–C bond leads to the formation of a betaine with a positive charge on the phosphorus atom and a negative charge on the carbon atom (Scheme 6.130).



Scheme 6.130

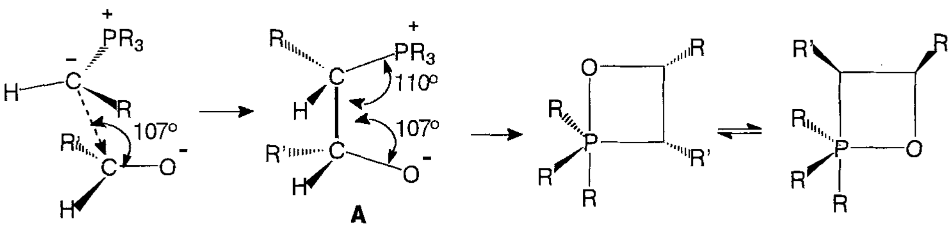
In the first instant after the formation of the betaine, its R and R′ substituents rearrange to the positions they occupy in the initial oxaphosphetane, and so elimination of triphenylphosphine oxide from the betaine affords the *cis* olefin. The substituents stabilizing the betaine (electron-donating groups on the phosphorus or electron-withdrawing groups on the ylidic carbon atom) increase the stability of betaine, however, and this undergoes rotation about the C–C bond to occupy the most energetically advantageous conformation with *trans* disposition of R and R′. Subsequent elimination of the triphenylphosphine oxide thus affords the *trans*-olefin.



Scheme 6.131

Bestmann synthesized polycyclic oxaphosphetanes with sterically hindered pseudorotation; these were found to be thermally stable compounds, confirming that the pseudorotation is a necessary process for the conversion of oxaphosphetanes to phosphine oxide and olefin (Scheme 6.131)[529]:

In agreement with Bestmann's concept the preferred orientation of the transition state leading to the *erythro* oxaphosphetane is approach of the ylide nucleophilic center to the carbonyl group at an angle of 107°, with the double bonds of both reagents arranged in one plane; this was associated with the Burgi–Dunitz trajectory concept (Scheme 6.132) [743]



Scheme 6.132

The conversion of reagents into oxaphosphetane requires minimum energy when it proceeds in one step with the non-synchronous formation of bonds between the carbonyl and ylidic carbon atoms. Bestmann showed, together with a computational evaluation of diastereomeric transition states, that **A** represent a 'quasi-betaine transition state' that does not lead to a betaine but to an oxaphosphetane[601,744].

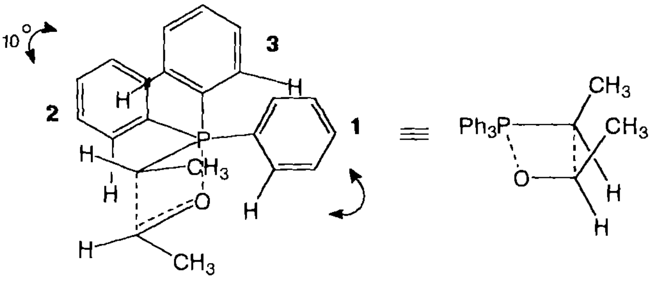
In the concerted cycloaddition category Shlosser and Schaub[733] have proposed a one-step mechanism in which a leeward approach of the reagents, with a planar transition state, would be responsible for the stereoselectivity. Shlosser and Schaub proposed a model of the transition state for the Wittig reaction between triphenylphosphonium ethylide and aldehydes which accounted for the predominant formation of the *erythro* oxaphosphetane. They proposed structure was based on the steric interactions between different groups of the oxaphosphetane ring ('leeward approach' model)[733]. On the assumption that these are kinetically controlled reactions Schlosser and Schaub used the contrast in selectivity between $Et_3P{=}CHR$ and $Ph_3P{=}CHR$ (Table 6.30) to propose a new basis for the origin of the stereoselectivity of the oxaphosphetane.

$$R_3P{=}CHMe + R'CHO \longrightarrow R'CH{=}CHMe{+}R_3PO \tag{6.267}$$

Table 6.30. Effect of the substituents R and R′ on the stereoselectivity of the Wittig reaction[733]

R'	R=Ph		R=Et	
	Yield (%)	*Z*: *E*	Yield (%)	*Z*: *E*
C_6H_6	95	86: 12	94	33: 67
t-Bu	92	92: 2	92	10: 90
Ph	94	87: 13	99	17: 83
$4\text{-}ClC_6H_4$	88	88: 12	89	4: 96

The *cis*-selective transition state for $Ph_3P{=}CHR$ reactions with aldehydes was illustrated by structure **B** and the source of this preference was attributed to steric interactions.



B

Figure 6.2

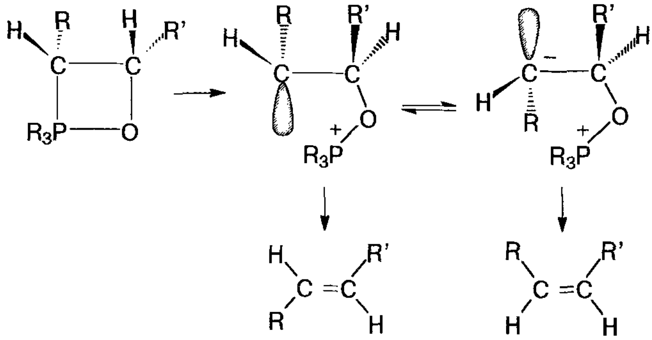
The authors[733] supposed that in ground state the *cis*-disubstituted 2,2,2-triphenyloxaphosphetane is sterically less congested than its *trans* stereoisomer. Indeed, at 0°C the *cis* adduct (R = R′ = Ph) is transformed into the olefin half as rapidly as the *threo* isomer of oxaphosphetane. Alternatively the *erythro* isomer of oxaphosphetane having R = Et and R′ = Ph, is decomposed five times faster at 25°C than the *trans* isomer.

The Schlosser model showed that in the transition state the formation of the *trans* oxaphosphetane is sterically less favorable than the *cis* oxaphosphetane, although the recently detected phenomenon of stereochemical drift detracts from this very interesting model[745]. It has been observed by low temperature ^{31}P NMR that the *cis* oxaphosphetane is transformed into the *trans* isomer, because the amount of *trans* olefin obtained was larger than the initial amount of the *trans* oxaphosphetane.

Stereochemical drift has not been observed for pure *trans* oxaphosphetanes and *cis* oxaphosphetanes cleave faster than the *trans* isomers. Consequently, *trans* oxaphosphetanes are thermodynamically more stable than the *cis* isomers and the transition state in the reaction of aldehydes with non-stabilized ylides cannot, therefore, be similar to product, whereas in the Shlosser model it is similar.

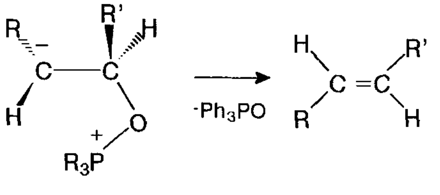
In the mechanism proposed by Bernardi and Whangbo the primary intermediates of the Wittig reaction are also *trans* oxaphosphetanes[746,747]. The principal transformation of oxaphosphetane consists in the cleavage of the C–P bond and the formation of a betaine. The carbanion is sp^3-hybridized if there is no direct mesomeric delocalization of the charge on the carbanion by substituent R. Rotation around the C–C bond results in the conversion of the primary formed rotamer of the betaine, with *syn* positioning of the free electron pair of the C–C bond in a rotamer with *anti* disposition of the free pair of electrons on the C=O bond. Rotation is accompanied by the substituents changing from the *trans* to the *cis* positions (Scheme 6.133):

To take into account the stereoelectronic advantages arising from the *anti* disposition of the free electron pair and the leaving group, they supposed that the elimination reaction must proceed with involvement of the second rotamer of betaine. As a result the *anti*-elimination leading to the *cis* olefin become predominant.



Scheme 6.133

The carbanion is planar and undergoes *cis*- and *anti*-elimination, if substituents at this anionic center delocalize the negative charge. The initially formed betaine with sterically advantageous *trans* substituents leads directly to the *trans* olefin (Eq. 6.268):



(6.268)

Even though all the mechanisms proposed for the Wittig reaction represent attempts to accommodate the experimental evidence, all remain essentially unsubstantiated. They are, furthermore, all based on subjective evaluation of how the steric strain in the *Z*-generating transition-state structure compares with that of its *E*-generating counterpart. The experimental evidence indicates that within the Wittig reaction path, the step that yields the oxaphosphetane seems to be the one that determines the stereoselectivity of the reaction. However it must be emphasized that there is no direct experimental evidence indicating the most likely nature of the transition state involved in the Wittig half reaction, and the failure to detect spectroscopically possible transient intermediates, such as betaine spin-paired diradicals[683,734,735] or charge-transfer complexes[735–739] cannot, furthermore, rule out their possible involvement in the Wittig reaction. The course of the Wittig reaction has been investigated by rapid application of ^{17}O , ^{13}C, and ^{31}P NMR spectroscopy[740]. A new dynamic equilibrium of oxaphosphetanes was observed for the first time[741].

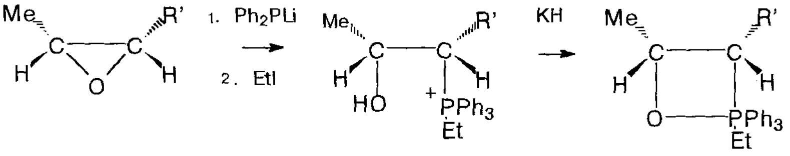
6.6.2 Modern Concept of the Wittig Reaction Mechanism

Detailed studies have resulted in the currently accepted mechanism of the Wittig reaction. The central moments of these studies were the stereochemistry and intermediates of the first step of Wittig reactions performed with stereochemically pure *cis* and *trans* oxaphosphetanes.

Although many of the puzzling features of the Wittig reaction mechanism have been clarified in recent years, it seems clear that no single mechanism explains the progress of the reaction and all its transition states and stereochemical intricacies. Accordingly, this section reviews the mechanisms for the Wittig reaction separately for non-stabilized, semi-stabilized, and stabilized ylides.

6.6.2.1 Non-stabilized Ylides

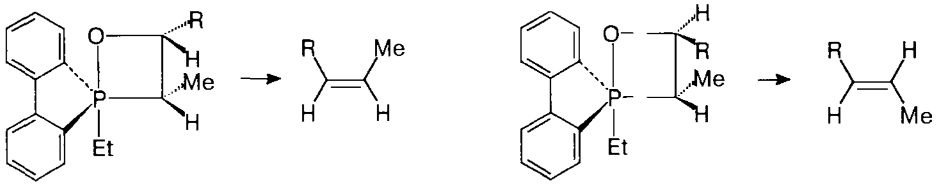
The *cis* and *trans* oxaphosphetanes were prepared by deprotonation of the *threo* and *erythro* isomers of *β*-hydroxyalkylphosphonium salts with the potassium hydride at low temperature in aprotic solvents. Highly stereospecific methods were developed for the synthesis of the stereochemically pure isomers of C-hydroxyphosphonium salts, in particular the reaction of *cis* and *trans* epoxides with lithium phosphides and subsequent quaternization of the formed phosphines with alkyl halides (Eq. 6.269)[731,748,749]. A review has been published on the synthesis and structures of Wittig reaction intermediates[750].



(6.269)

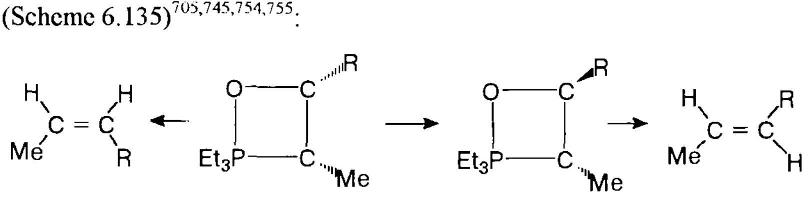
Vedejs and coworkers[731] gave evidence of the stereospecific conversion of oxaphosphetanes into olefins. They reported that the reaction of epoxides with tertiary phosphines proceeds via the formation of an oxaphosphetane as intermediary product. It is well-known that epoxides with the *cis* configuration are the precursors of *trans* oxaphosphetanes whereas the *trans* epoxides afford *cis* oxaphosphetanes. Indeed the reaction of tri-*n*-butylphosphine with *cis*-but-2-ene oxide gave a *trans* oxaphosphetane which was the direct precursor of *trans*-but-2-ene– confirming the selective transformation of oxaphosphetanes into olefins[751].

Unlike the results of previously reported investigations, these new results indicated that *cis* and *trans* oxaphosphetanes exist in equilibrium with the starting compounds—the isomers of oxaphosphetanes prepared by deprotonation of α-hydroxyalkylphosphonium salts are conformationally stable compounds. For instance, the *cis* and *trans* isomers of oxaphosphetanes bearing a dibenzophosphole ring had remarkable thermal stability and did not isomerized on heating to 70–110°C. At higher temperatures they are gradually converted into olefins. The reaction resulted in 99% stereospecificity to provide stereochemically pure *Z* and *E* olefins, implying the irreversibility of the first step of the Wittig reaction (Scheme 6.134) [730,751,753]



Scheme 6.134

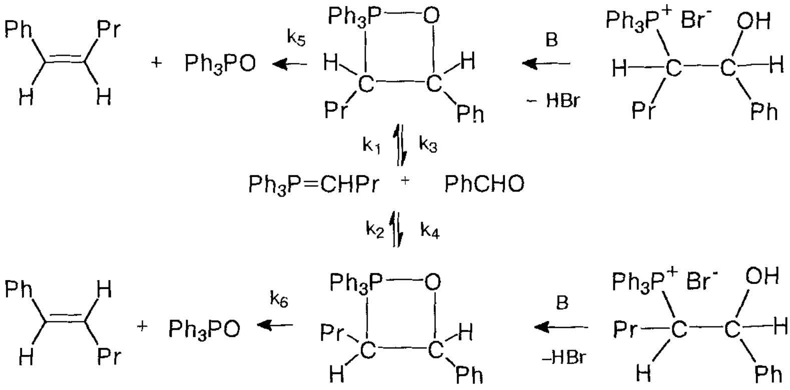
Maryanoff and Reitz discovered the stereochemical drift of *cis* oxaphosphetanes into their *trans* isomers. The stereochemical drift of *cis* oxaphosphetanes in the presence of an admixture of the *threo* isomer was intensified by synergism to result in *cis* and *trans* olefin mixtures enriched with the *trans* isomer[745]. The *trans* isomers were not transformed into the *cis* isomers and did not undergo stereochemical drift. Evidently *trans* oxaphosphetanes are thermodynamically more stable than *cis* oxaphosphetanes (Scheme 6.135)[705,745,754,755]:



Scheme 6.135

Marrianoff and coworkers discovered by means of kinetic studies that the rate of retro-decomposition of *cis* oxaphosphetanes into ylide and benzaldehyde is 7–15 times faster than the rate of retro-decomposition of *trans* oxaphosphetanes.

Marrianoff supposed that the first step of the Wittig reaction is reversible for *cis* and *trans* olefins (Scheme 6.136) and that the second step of the reaction is rate-determining. So, decomposition of the oxaphosphetanes proceeds in two directions to ylide and aldehyde or to olefin and phosphine oxide.



Scheme 6.136

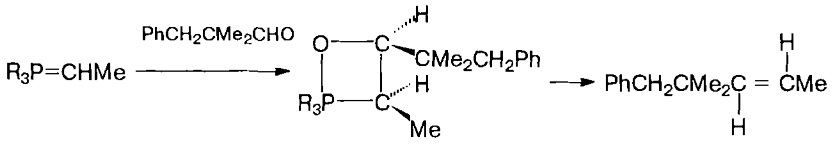
These reaction routes correspond to dynamic states—of the balance of relative rates of every of two steps. Ab initio quantum-chemical calculations accomplished by Volatron and Eisenshtein[726,756] provide evidence that transformation of oxaphosphetane into alkenes and phosphine oxides is a *supra,supra*-concerted decomposition of a cyclic system consisting of four coplanar heavy atoms. The activation energy of such a decomposition is 121 kJ mol^{-1}.

Oxaphosphetane intermediates in the Wittig reaction are more energetically advantageous than betaines. Volatron and Eisenshtein[726,756] calculated the energetic profile of the reaction between $H_3P{=}CH_2$ and formaldehyde, and found that activation energy E_a of formation of oxaphosphetane with the oxygen atom in the axial position is 29 kJ mol^{-1} whereas E_a for betaine was 134 kJ mol^{-1}. They concluded that betaine (in the *anti* form) is not an intermediate of the Wittig reaction and probably represents one of the maxima on the theoretical free-energy profile for the reaction, leading to phosphine and ethylene oxide. Volatron visualized two eventual directions of decomposition of oxaphosphetane—to phosphine oxide and alkene (the Wittig reaction) or to phosphine and epoxide (the Corey–Chaikovski reaction). The calculation showed that the formation of alkene and phosphine oxide is energetically more advantageous than the formation of phosphine and epoxide.

The results obtained by Volatron and Eisenshtein are in general agreement with the conclusions of Holler and Lishka[727]. These authors performed the ab initio SCF (STO-3G) calculations on the model Wittig reaction of $H_3P{=}CH_2$ with formaldehyde. In this work the mechanism of the reactions was visualized as [2+2]-cycloaddition without the formation of a betaine. The formation of the oxaphosphetane proceeded, via a very low energetic barrier, on the theoretical free-energy profile. MNTO calculations for reaction of $H_3P{=}CHMe$ and $Me_3P{=}CHMe$ with acetaldehyde showed that the betaine is less energetically stable than the oxaphosphetanes (by 83 kJ mol^{-1}) and is, therefore, not formed. It was also found that *trans* oxaphosphetanes are energetically more stable than *cis* oxaphosphetanes. The transition state leading to the *trans* olefin was energetically more favorable than that resulting in the *cis* olefin.

The calculations of Holler and Lischka confirmed the idea of concerted reaction and define the activation energy of decomposition to ethylene and phosphine oxide (105 kJ mol^{-1})[727]. Marrianoff obtained a similar experimental value for the activation energy ($\Delta G^{\neq}$ for the *cis* and *trans* isomers = 79.1 and 78,6 kJ mol^{-1} at −30°C), confirming the theoretical prediction of the concerted decomposition of oxaphosphetanes[705,754].

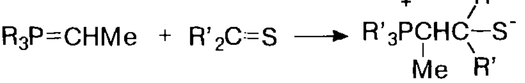
Vedejs and Marth[757] showed that the rate of pseudorotation of oxaphosphetanes bearing dibenzophosphole ring is 108 times faster than the rate of decomposition of oxaphosphetanes in the Wittig reaction, hence the pseudorotation is not a rate-determining step of decomposition. The activation barrier for decomposition of oxaphosphetane to olefins also does not depend on pseudorotation. Vedejs and March came to the conclusion that the conversion of oxaphosphetane to alkene is a non-synchronous decyclization with outstripping cleavage of P=C bonds. Vedejs supposed that the cleavage of oxaphosphetanes to starting compounds is possible only rarely and in principle should not be assumed without special evidence. Reliable reversibility of the first step of the Wittig reaction was shown only in the crossover experiment of the reaction of triphenylphosphonium ethylide with aromatic aldehydes[729]. Examples of both Z- and *E*-selective formation of oxaphosphetanes under the kinetic control of the first step of the Wittig reaction were reported (Eq. 6.270). For instance, some trialkylphosphonium and mixed alkylphenylphosphonium alkylides react with *tert*-alkylaldehydes without stereochemical equilibrium to afford *trans* oxaphosphetanes which are converted into alkenes with high proportion of *trans* olefins (*Z*:*E* = 95:5)[731].



(6.270)

R$_3$P=Ph$_3$P, Ph$_2$EtP

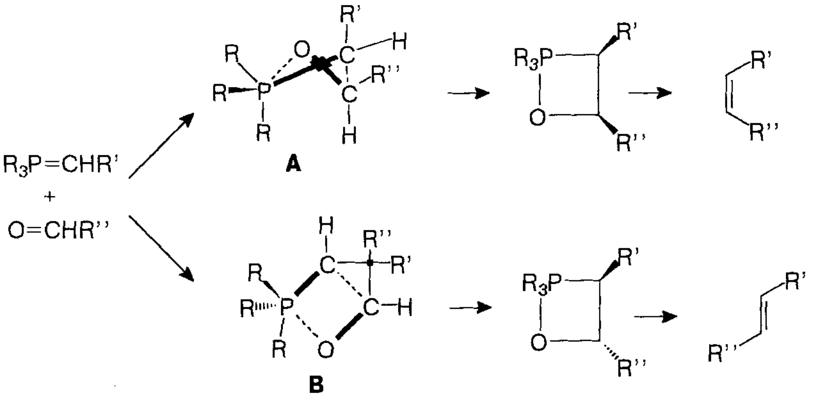
Vedejs showed experimentally that the first step of the Wittig reaction proceeds under the kinetic control to result, depending on the structure of starting compounds and on the reaction conditions, in *cis* or *trans* oxaphosphetanes. Oxaphosphetanes were obtained as primary intermediates of the Wittig reaction as a result of the direct asynchronous [2+2]-cycloaddition of ylides to carbonyl compounds. The mechanism does not take into account the formation of betaines as oxaphosphetane precursors. A Russian group recently reported the first evidence in the reaction of non-stabilized ylides with a Michler thioketone (Eq. 6.271)[742]:



$$R_3P{=}CHMe + R'_2C{=}S \longrightarrow R'_3\overset{+}{P}\underset{Me}{C}H\overset{R'}{\underset{R'}{C}}{-}S^- \qquad (6.271)$$

R=Et, Ph; R'=C$_6$H$_4$NMe$_2$-4

The cycloaddition proceeds under the conditions of dominant kinetic control. 1,2-*cis* steric interactions between the substituents of the R′ ylide and the R″ aldehyde or 1,3-steric interactions between R′ and nearest phosphorus ligand in the four-membered transition state (Scheme 6.140 **A** or **B**) are main factors defining the selectivity of the formation of oxaphosphetanes.



Scheme 6.137

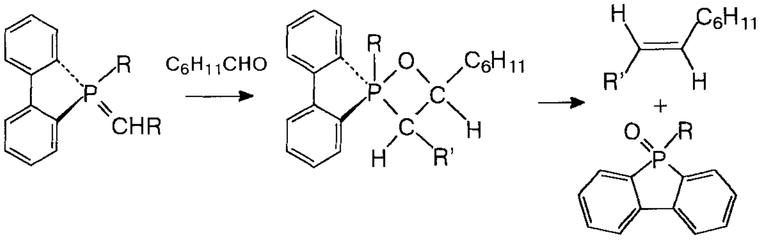
The parallel approach of the ylide to the carbonyl compound is hampered, because the phosphorus atom is sp^3-hybridized and one of its substituents is directed toward the approaching aldehyde. Therefore some distortion in transition state can reduce phenyl–oxygen interaction. Compromise between 1,2 and 1,3 interactions of substituents under the conditions of kinetic control defines the transition states **A** or **B**, leading to *cis* or *trans* oxaphosphetanes (Scheme 6.137).[664] For non-stabilized triphenylphosphonium ylides the most advantageous transition state is a compact four-membered cyclic system with the R group of the aldehyde and the R″ group of ylide both pseudo-equatorial. The *cis*-selectivity of oxaphosphetane formation increases in the sequence R_3CCHO > R_2CHCHO > RCH_2CHO as the volume of the substituent R″ is increased.

The stereoselectivity of the Wittig reaction of aromatic ketones with non-stabilized phosphonium ylides depends on the substituents on the aromatic ring[758].

6.6.2.2 Semi-stabilized Ylides

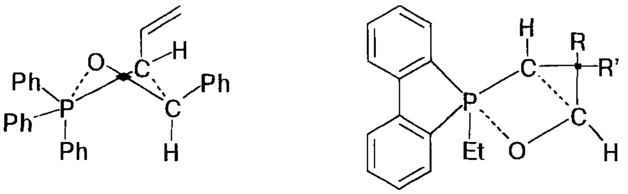
Investigation of the mechanism of the Wittig reaction for semi-stabilized and stabilized ylides is more difficult because the first step of reaction is rate-determining. The intermediates form slowly, during the reaction of ylide with aldehyde, then decompose readily to olefin and phosphine oxide. Even at very low temperatures oxaphosphetanes are immediately decomposed to olefin and phosphine oxide, because electron-accepting substituents destabilize the oxaphosphetane ring.

Recently Vedejs has detected the oxaphosphetanes formed by reaction of dibenzophosphole ylides with aldehydes[732,758]. Oxaphosphetane stability in this reaction is determined by the extent of destabilization of the tetrahedral phosphorus atom which results from reduction of the C–P–C angle of the five-membered ring to 90–94°. Dibenzophosphole ylides reacted with aldehydes at –78°C to result in oxaphosphetanes, which were detected by NMR. At –50°C in 10 min half the oxaphosphetane was converted into olefin and phosphine oxide (Scheme 6.138):



Scheme 6.138

Deprotonation of β-hydroxyalkylphosphonium salts provides analogous *cis* and *trans* oxaphosphetanes, which are conformationally stable and are not transformed into olefins at temperatures up to that of decomposition (–50°C). Every one of these isomers is converted into the *cis* or *trans* isomers of the appropriate olefin with 95–99% stereospecificity. Electron-accepting substituents R′ reduce the activation barriers of conversion of oxaphosphetanes to olefins to 33–42 kJ mol^{-1} because, as has been shown by quantum-chemical calculations, C–P bonds in the transition states which lead to the olefins are stretched in some extent. Evidently, the extent of 1,2 steric interactions (leading to planar structure I) or 1,3-interactions (leading to compact structure A) influences the formation of the transition state; the *cis* or *trans* oxaphosphetanes which are formed as a result of these interactions are subsequently converted into *cis* or *trans* olefins, respectively. For semi-stabilized ylides the compact, **A**, or planar, **B**, transition state are possible, depending on the substituents R^{1}and R^2 of the ylide and R^3 of the aldehyde. Thus, the reaction of salt-free triphenylphosphonium allylides with benzaldehyde is *cis*-selective. The compact four-membered transition state predominates over the planar structure **B**, because of significant 1,3 interactions between substituents R and R′. The presence of dibenzophosphole ring in the ylide molecule reduces the C–P–C ring angle and facilitates the parallel approach of the C=P and C=O groups, thus creating favorable kinetic conditions for *E*-selectivity (Scheme 6.139)[732,758]:

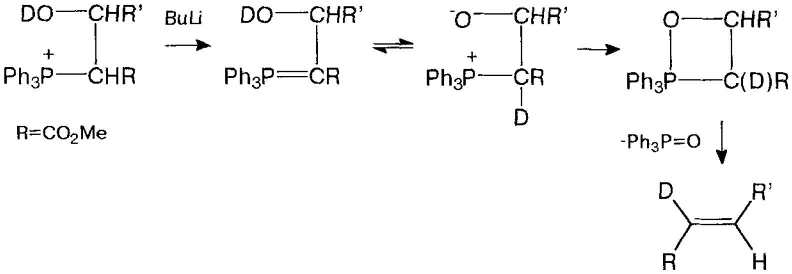


Scheme 6.139

Di Donxia and coworkers[759] studied the kinetics of the reaction of triphenylphosphonium benzylides with substituted aromatic aldehydes. Electron-accepting substituents on either benzaldehyde or on triphenylphosphonium benzylide increased the rate of the reaction. On the basis of kinetic data and interconversions of the linear free energies of the Wittig reaction they proposed a mechanism which included the formation of a betaine and a four-membered cyclic transition state[759]. The relative reactivity and stereoselectivity of the Wittig reaction of substituted benzaldehydes with benzylidene triphenylphosphorane has been reported[737]. Kawasima and coworkers recently described a novel route to isolable 1,2-oxaphosphetanes and the mechanism of their thermolysis in the second step of the Wittig reaction[760].

6.6.2.3 Stabilized Ylides

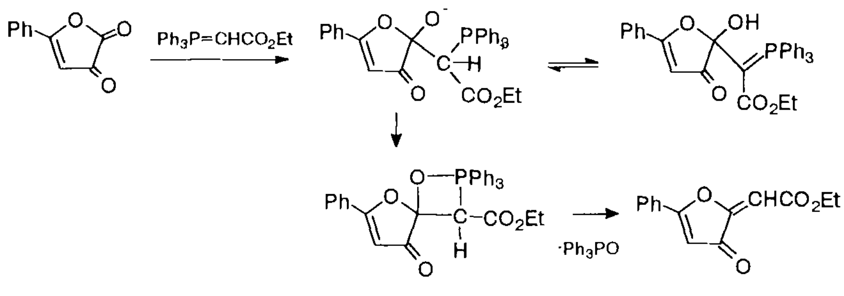
Detailed studies of the Wittig Reaction of stabilized ylides with carbonyl compounds have led to the proposal of the formation of betaines as primary intermediates which are then transformed to oxaphosphetanes. For instance, the deprotonation of deuterated α-hydroxyalkylphosphonium salts by strong bases (butyllithium) leads to the formation of deuterated olefins, i.e. deuterium migrates from the oxygen atom to the carbon. It is, therefore, *likely that unstable α-hydroxy ylides are formed and that these, as a result of* deutero-exchange, are transformed into betaines containing deuterium on the endocyclic carbon; these then decompose to furnish deuterated olefins. Deprotonation of salts by weaker bases (DBU) affords only non-deuterated olefins (Scheme 6.140)[732]:



Scheme 6.140

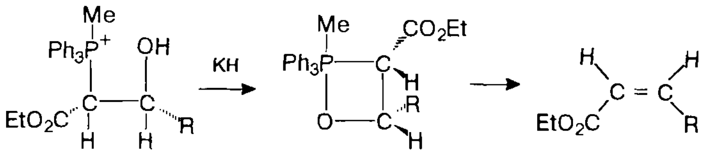
The author and coworkers have reported a reaction confirming this mechanism (Scheme 6.141)[761]. Oxazolidinedione reacts with triphenylphosphonium carboethoxymethylide with the formation of hydroxy ylides which are stable in the crystalline state and which have been isolated and characterized. In solution, because of a tautomeric equilibrium between the hydroxy ylide and the betaine intermediate, the classic Wittig reaction results in an olefin and phosphine oxide

Analysis of the experimental results from the reaction of stabilized ylides with carbonyl compounds, leads to the assumption that a betaine is formed as a primary intermediate in the Wittig reaction[732]. Vedejs, however, discounts the possibility that the equilibrium between the oxaphosphetane and the betaine proceeds with cleavage of C=P bonds

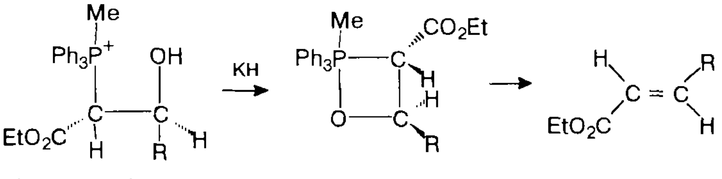


Scheme 6.141

E-Selective reactions of ethoxycarbonyl-stabilized ylides in aprotic solvents (benzene, THF, DMFA) in mechanism, proposed by Vedejs, can be described as non-concerted cycloaddition, analogous to those occurring with non-stabilized ylides. The planar four-membered transition state is more preferential for stabilized ylides. Vedejs's proposals do not invoke equilibrium processes to explain the *E*-selectivity of the reaction. Experimental data provide convincing evidence for the irreversibility of the first step of the Wittig reaction with stabilized ylides (Eq. 6.272; 6.273)



(6.272)



(6.273)

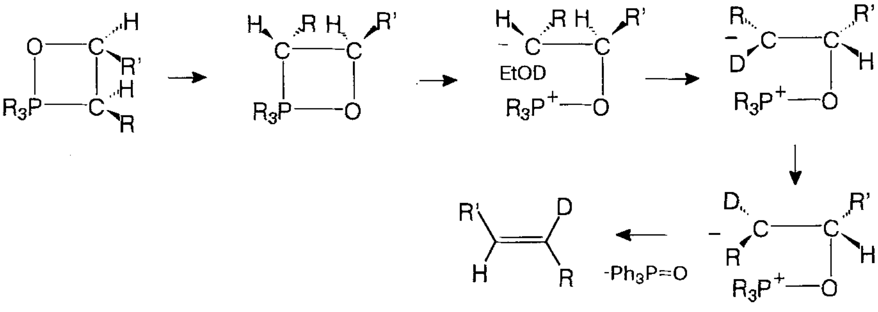
R=c-Hexyl

Deprotonation of stereochemically pure *threo* and *erythro* isomers of *β*-hydroxyalkylphosphonium salts by the potassium hydride at 90°C afford stereochemically pure *cis* and *trans* olefins with 95% stereospecificity[762].

Reaction of triphenylphosphonium ethoxycarbonylmethylide with cyclohexylcarboxaldehyde results in the formation of olefin with a *Z*:*E* isomer ratio of 5:95. Consequently, the Wittig reaction of stabilized ylides with aldehydes proceeds under the conditions of kinetic control. *E*-Selectivity of the Wittig reaction results from selective formation of *trans* oxaphosphetanes. The presence of electron-accepting substituents does not stabilize but, on the contrary, destabilizes the intermediary products and accelerates the decomposition of the oxaphosphetane.

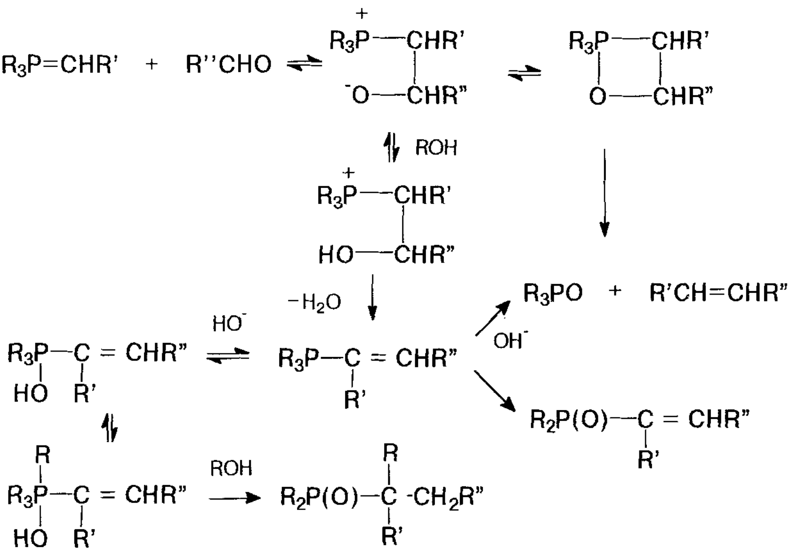
6.6.2.4 The Wittig Reaction in Protic Media

The preferential formation of *trans* olefins in protic solvents was reported for the first time by Schlosser and Christmann in 1967. They explained the phenomenon in terms of the influence of solvent on the solvation of the betaine and an increase in the reversibility of the first step of the Wittig reaction[647]. This idea was further developed by Bottin-Strzalko, Seyden Penne, and Tchoubar[763,764] An analogous mechanism accounting for the formation of oxaphosphetanes during the Wittig reaction with alcohols, was proposed by Aksnes and coworkers on the basis of kinetic studies[718,719] The formation of deuterated olefins during the Wittig reaction in deuteroethanol medium gave reason to Bestmann to propose a mechanism visualizing oxaphosphetanes as reaction intermediates (Scheme 6.142) [765]:
Betaines bearing a negative charge on the carbon and a positive charge on the phosphorus are direct precursors of olefins. Deutero-exchange proceeds in deuteroethanol and results in a change in the configuration of the carbanion. The new betaine has a configuration with the substituents on the carbon atom in the transoid position and the free electron pair interacting with positively charge phosphorus atom. *syn*-Elimination of phosphine oxide results in the formation of the olefin with *trans* configuration containing the deuterium.



Scheme 6.142

Allen and coworkers[766] proposed a mechanism, taking into account the protonation of betaine in protic media, for the formation of oxaphosphetanes starting from a betaine and a phosphonium salt. As shown in the Scheme 6.143, the betaine can cyclize with the formation of an oxaphosphetane, or it can be protonated by the solvent. The first route leads to the olefin. The second, tentative, route explains the formation of phosphonates in proton-containing solvents:[766–769]. The authors[766] succeeded in increasing the conversion of oxaphosphetane into alkene by replacing the phenyl group on the phosphorus atom by a stronger electron-acceptor which, by destabilizing the betaine, promotes the formation of oxaphosphetane and thereby formation of the alkene:



Scheme 6.143

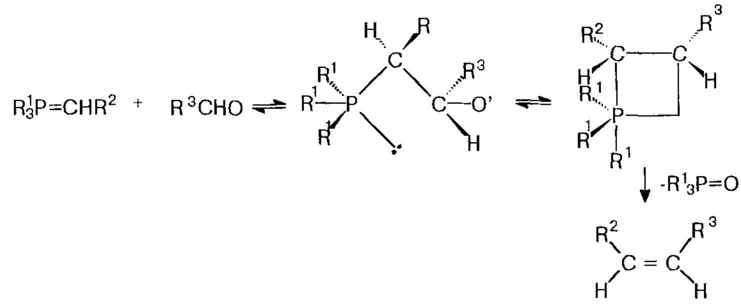
Chen and coworkers reported that the Wittig reaction of Cl_3CCHO or $Cl_3CH(OH)OMe$ with $Ph_3P{=}CHCO_2Me$ in methanol afforded $Cl_3CCH{=}CHCO_2Me$ whereas reaction with MeOD as a solvent furnished $Cl_3CCH{=}CDCO_2Me$. A mechanism involving proton–deuterium exchange between a reaction intermediate and the solvent was postulated to explain the solvent participation[770].

6.6.2.5 Single-Electron-Transfer Mechanism

Several groups have proposed a single-electron-transfer mechanism for the Wittig reaction. In the first step the formation of the radical–ion pair has been invoked.

A stepwise mechanism for the Wittig reaction involving electron transfer from the ylide to the aldehyde has been proposed by Olah and Krishnamurthy[771], although insufficient evidence was collected to support the proposal. The authors suppose that electron transfer can also occur with other carbonyl compounds (Scheme 6.144).

This idea was developed by Yamataka and coworkers[736], who proved experimentally that the reaction of triphenylphosphonium isopropylide with benzaldehyde proceeds with electron transfer. They also reported a study of a carbon isotope effect in the reaction and found that addition of non-stabilized ylides to aldehydes resulted in oxaphosphetane formation which proceeded via a initial electron transfer step from the ylide to the carbonyl group[736]. The reaction of triphenylphosphonium isopropylide with ^{14}C-benzaldehyde proceeded with a positive kinetic isotope effect under both Li salt-free conditions ($k^{12}/k^{14} = 1.060$) and in the presence of Li salt ($k^{12}/k^{14} = 1.015$) (Table 6.31).



Scheme 6.144

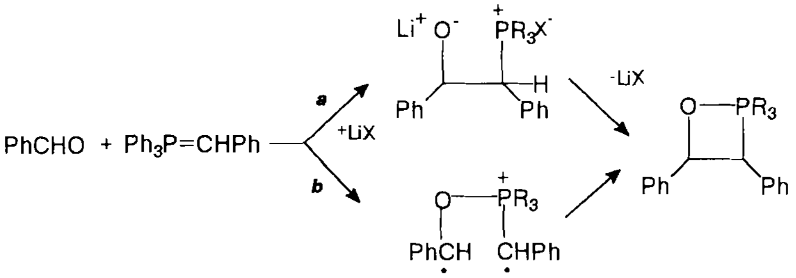
Table. 6.31. Carbon-14 kinetic isotope effect in the reaction of PhCHO with P-ylides[737]

Ylide	Base	$^{12}k/^{14}k$
$Ph_3P=CHPh$	NaHMDS	1.060±0.003
$Ph_3P=CHPh$	LiHMDS	1.015±0.004
$Ph_3P=CMe_2$	NaHMDS	1.003±0.002

The main kinetic characteristic of the reaction of triphenylphosphonium isopropylide with benzaldehyde was analogous with that of the reaction of triphenylphosphonium methylide with benzaldehyde, which also proceeds via an electron-transfer mechanism. These, together with the absence of enone isomerization for the benzylidene ylide reported previously, suggested that the reactions proceed via a polar cycloaddition transition state of considerable nucleophilic character[737]. The electron-transfer step is rate determining for benzaldehyde whereas radical coupling after the electron transfer step is rate-determining for benzophenone[735–739].

The various single-electron-transfer mechanisms have distinct implication for the stereochemistry-determining step of the Wittig reaction. McEwen and coworkers[683,734] found that the Wittig reaction proceeds with the formation of a spin-pair diradical intermediate when sodium or potassium ions are present but that an ionic reaction occurs when lithium ions are present. The reaction occurs under kinetic control, without any significant amount of equilibrium or Wittig reversal (Scheme 6.145).[735]

As for the Wittig reaction with stabilized ylides, with an ylide of moderate stability the stereochemistry (*E*:*Z* ratio) of alkene formation with an aldehyde is determined at the point that the new carbon–carbon bond is formed to give a betaine or an oxaphosphetane intermediate. The observed stereoselectivity of the olefination is determined by the steric interactions between the substituents of the ylide and carbonyl compound during the formation of the spin-pair diradical.



Scheme 6.145

* * *

So, analysis of available experimental and theoretical data leads to the conclusion that the Wittig reaction does not proceed by a uniform mechanism. The structures of the reagents, the reaction medium, the solvents present, and the presence of lithium salts all influence the reaction mechanism. Evidently study of the Wittig reaction mechanism, despite great successes in this area, must be continued. The great significance of the Wittig reaction encourages the hope that new experimental data which clarify the details of its mechanism will soon become available.

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Phosphorus Ylides: Chemistry and Application in Organic Synthesis
by Oleg I. Kolodiazhnyi
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Conclusion and Final Remarks

This book has illustrated the breath and scope of the development of phosphorus ylide chemistry since its discovery 80 years ago. Besides the synthesis of novel structural types and the discovery of new means of interpreting reactions, phosphorus ylides have introduced some novel reactions

The versatile reactivity of phosphorus ylides enables their use as starting reactants in the synthesis of many important organic compounds. The synthetic utility of the phosphorus ylides as highly effective reagents for organic synthesis is most clearly shown by their reaction with carbonyl compounds (the Wittig reaction).

During recent years the chemistry of phosphorus ylides has been extensively developed, their chemical properties have been studied in detail, and areas of their practical application in organic synthesis have been discovered. Because of their unique molecular and electronic structure, phosphorus ylides undergo a wide variety of reactions. Some of these reactions are typical of the carbanion nature of ylides in general. The phosphonium group has little effect on such reactions and participates only as an electron-withdrawing substituent attached to the carbanion. Other reactions depend on the unique phosphorus ylide structure and involve both the carbanion and phosphonium parts of the ylide.

Phosphorus ylides attract particular interest as reagents for organic synthesis, and thus find increasing application in laboratory practice and industry. The most important and useful reaction of phosphorus ylides is certainly their reaction with carbonyl compounds, which enables the preparation of alkenes. Other reactions of phosphorus ylides, which are important synthetic tools of organic synthesis, have been discussed.

Phosphonium ylides are accessible compounds which can be obtained by simple methods from cheap chemical reagents. This accessibility of phosphorus ylides is the reason for the intensive studies of their chemical properties that have led to the wide extension of the ylides both in preparative chemistry and in industrial fine organic synthesis.

Although some excellent and synthetically promising work devoted to asymmetric reactions of phosphorus ylides has been published, the development of more efficient methods in this area is necessary—for example the application of chiral catalysts or dynamic kinetic resolution of carbonyl compounds.

Heteroatoms on the ylide carbon atom have a considerable effect on the chemical properties and reactivity of the phosphorus ylides. Certain heteroatoms, such as the atoms of the main Groups I and II, and nitrogen, tin, and lead atoms, increase the electron density on the carbon atom, and thereby the reactivity of ylides, whereas, in contrast, other heteroatoms such as silicon and germanium atoms, Group V–VII atoms, and transition elements, stabilize the ylide carbanion, thus reducing its nucleophilicity. As a result, C-substituted phosphorus ylides acquire remarkable new chemical properties and offer new synthetic opportunities. This explains the deep interest of chemists in C-hetero-substituted phosphorus ylides as exceptionally promising reagents in organic synthesis[484].

Compounds with optical activity because of the presence of an asymmetric phosphorus center are accessible and can be relatively easily obtained.

The greatest progress has been in the area of natural compound synthesis and the power of the Wittig reaction and related reactions in chemical synthesis is amply demonstrated by the widespread application of this reaction in the total synthesis of naturally occurring products. Because of the enormous task required for complete coverage of the literature we have covered only several selected examples of the application of such reactions.

We hope that this book will be useful to chemists interested in various aspects of synthetic organic and inorganic chemistry. The material, and problems, discussed provide numerous possibilities for the application of phosphorus ylides in the synthesis of variety of important biologically active compounds.

Looking to the future it might be said that phosphorus ylides will be, and should be, the subject of further studies, and we await the further development of the application of phosphorus ylides. Further studies might be dedicated to the stereochemistry of the Wittig reaction and to the synthesis of biologically active compounds.

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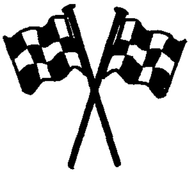

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Oleg I. Kolodiazhnyi

Phosphorus Ylides

Nobody could have imagined how useful and versatile phosphorus ylides could be, when Wittig first developed and described this class of compounds. This book provides a comprehensive and up-to-date compilation of the chemistry and applications of phosphorus ylides in organic synthesis. Phosphorus ylides are discussed as reagents in the synthesis of a broad range of substances, amongst them olefins, acetylenes, cyclic and heterocyclic compounds, naturally occuring compounds like pheromones, steroids and carotenoids, and pharmaceutically and biologically active compounds such as antibiotics and prostaglandins.

A special beneficial feature of this book is about 150 key experimental procedures with all necessary data. So bitten by the new idea you can start immediately on the preparation without having an extremely time-consuming literature search. But should the search be inevitable, about 2500 references (till 1998) supply an easy access to the primary literature.

No doubt, every chemist in academia and industry working in organic, bioorganic, inorganic, and medicinal chemistry will welcome this book as an inspiration of concepts, ideas and practical syntheses.

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