Oleg I. Kolodiazhnyi

Phosphorus Ylides

Chemistry and Application in Organic Synthesis

This Page Intentionally Left Blank

Oleg I. Kolodiazhnyi

Phosphorus Ylides

WILEY-VCH

Further Titles of Interest

K. Rück-Braun, H. Kunz
Chiral Auxiliaries in Cycloadditions
1999, ISBN 3-527-29386-8

F. Diederich, P. J. Stang (Eds.)
Metal-catalyzed Cross-coupling Reactions
1998, ISBN 3-527-29421-X

Y. Chapleur (Ed.)
Carbohydrate Mimics
Concepts and Methods
1998, ISBN 3-527-29526-7

H. A. Staab, H. Bauer, K. M. Schneider
Azolides in Organic Synthesis and Biochemistry
1998, ISBN 3-527-29314-0

Oleg I. Kolodiazhnyi

Phosphorus Ylides

Chemistry and Application
in Organic Synthesis

⊛ WILEY-VCH

Prof. Dr. Oleg I. Kolodiazhnyi
Institut of Bioorganic Chemistry
National Academy of Sciences
1, Murmanskaya Street
253660, Kiev-94
Ukraine

To my daughters, Anastasia and Olga

This Page Intentionally Left Blank

Contents

List of Abbreviations

1-Ad	adamant-1-yl		HMPT	hexamethylphosphotriamide
Alk	alkyl		i-Pr	isopropyl
All	allyl		IR	infrared
Ar	aryl or aromatic		kg	kilogram
Ar*	2,4,6-tri-tert-butylphenyl		L	liter
bp	boiling point		liq.	liquid
br	broad		LT	leukotrienee
Bu	butyl		m-	meta-
i-Bu	tertiary butyl		m	multiplet
s-Bu	secondary butyl		M	molar
t-Bu	isobutyl		Me	methyl
Bz	benzyl		Me₃Si	trimethylsilyl
cat.	catalyst		Mes	2,4,6-trimethylphenyl (mesityl)
cm	centimeter		mL	milliliter
Cp	cyclopentadienyl		mm	millimeter
Cp*	pentametylcyclopentadienyl		mp	melting point
*	centre of chirality		Mnt	menthyl
d	doublet		MS	mass spectrum
DBN	1,5-diazobicyclo[4,3,0]non-5-ene		n-	normal
DBU	1,8-diazobicyclo[4,4,0]undec-7-ene		N	normal (concentration)
			nm	nanometer
dd	double doublet		NMR	nuclear magnetic resonance
dec.	decomposition		o-	ortho-
diglyme	bis(2-methoxyethyl)ether (ethyleneglycoldimethylether)		p-	para-
			Pnt	pentyl
			PG	prostaglandin
DME	1,2- dimethoxyethane		Ph	phenyl
DMF	dimethylformamide		Pr	propyl
DMSO	dimethyl sulfoxide		i-Pr	isopropyl
dq	double quartet		Rₓ	perfluoroalkyl
dt	double triplet		q	quartet
Et	ethyl		s	second or singlet (NMR)
eV	electron volt		s- or sec-	secondary
Fc	ferrocen		sept	septet
FVP	flash-vacuum pyrolysis		t- or tert.-	tertiary
FVT	flash-vacuum thermolysis		THF	tetrahydrofuran
g	gram		TMEDA	tetramethylethylenediamine
h	hour		Ts	4-MeC₆H₄SO₂ (tosyl)
Hlg	halogen		UV	ultraviolet

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.

$$[Ph_3PMe]^+Br^- \xrightarrow{\text{PhLi}} Ph_3P=CH_2 \xrightarrow{\text{Ph}_2C=O} Ph_2C=CH_2 \qquad (1)$$
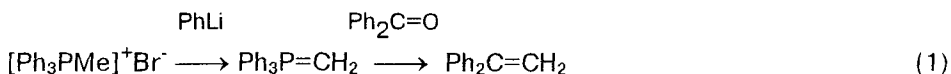
This discovery led to the development of a new method for the preparation of alkenes which has since found widespread application in synthetic organic chemistry and is

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.

Organic Phosphorus Ylides

$Me_3P=CH_2$ $Ph_3P=CHCH=CH_2$ $Ph_3P=CHPh$ $Ph_3P=CHCH=O$

C - Heterosubstituted Phosphorus Ylides

$Ph_3P=CHOMe$ $Me_3P=CHSiMe_3$ $Ph_3P=CCl_2$ $Ph_3P=CHPPh_2$

P- Heterosubstituted Phosphorus Ylides

$(Et_2N)_3P=CH_2$ $(PhO)_3P=CH_2$ $H_3P=CH_2$ $Et_2NP(F_2)=CH_2$ $(R_2N)_2P(Cl)=CH_2$

Carbodiphosphoranes and phosphacumuleneylids

$R_3P=C=PR_3$ $Ph_3P=C=C=C=CH_2$ $R_3P=C=C=X$ $Ph_3P=C=CF_2$

C- Metalated Phosphorus Ylides

$Ph_3P=CHLi$ $R_2P=CR'_2$ $Ph_3P=CHHg[N(SiMe_3)_2]_2$ $Me_3P=CH-U$

$\overset{|}{C}H_2Li$
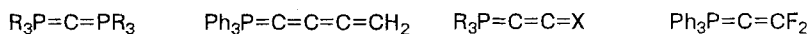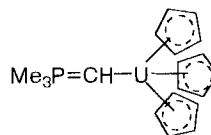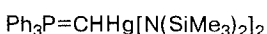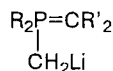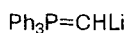
Cyclic Phosphorus Ylides
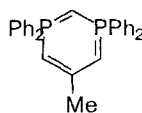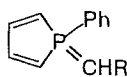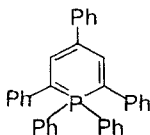
Scheme1

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 c'ass 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**.

$$\begin{matrix} R & & & R & \\ & \diagdown & & & \diagdown \\ R\!-\!\!\!-\!\!P\!=\!CR'_2 & \longleftrightarrow & R\!-\!\!\!-\!\!\overset{+}{P}\!-\!\overset{-}{C}R'_2 \\ & \diagup & & & \diagup \\ R' & & & R' & \end{matrix} \qquad (2)$$

A   **B**
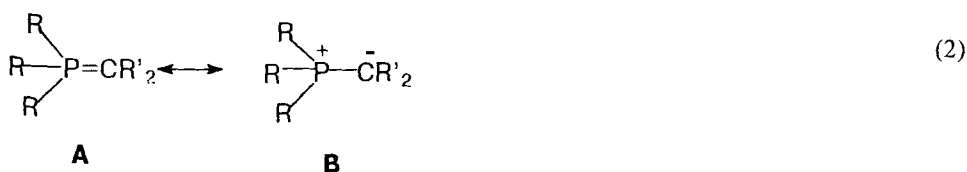
The first of these canonical structures (ylenic formula **A**) postulates the existence of double bonding between the phosphorus and carbon atoms. The second (ylidic formula **B**) reflects the highly polar zwitterionic nature of the ylidic P=C group and is a consequence of the existence of phosphonium 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 $(d–p)_\pi$ 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$_3$P=CR'$_2$

1

2
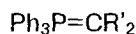
triphenyl-methylenephosphorane   *triphenyl-fluorenylenephosphorane*
triphenylphosphonium methylide   *triphenylphosphonium fluorenylide*
triphenylphosphonium methanide   *triphenylphosphonium fluorenide*

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].

References

1. Wittig, G. *Science,* **1980**, *210*, 600–604.
2. Bestmann, H.J., Zimmermann, R. *Organic Phosphorus Compounds.* Ed by G.M. Kosolapoff, L. Maier. Wiley–Intercience: New York, 1972, 1–184.
3. Schmidbaur, H. *Acc. Chem. Res.* **1975**, *8.* 62–70.
5. Bestmann, H.J., Vostrowsky, O. *Top. in Curr. Chem.* **1983**, *109*, 85–163.
6. Kolodiazhnyi, O.I., Kukhar, V. *Rus. Chem. Rev.* **1983**. *52*. 1096–1112.
7. Kolodiazhnyi, O.I. *Rus. Chem. Rev.,* **1991**, *60*, 391–409.
8. Kolodiazhnyi, O.I. *Tetrahedron,* **1996**, *52*, 1855–1929.
9. Maryanoff, B.E., Reitz, A.B. *Chem. Rev.* **1989**, *89*, 863–927.
10. Pommer, H., Thieme, C. *Top. Curr. Chem.* **1983**, *109*, 165–188.
11. Schlosser, M. *Top. in Stereochem.* Ed by E.L. Eliel, N.L. Allinger. 1970, Vol. 5, P. 1.
12. Johnson, A. *Ylides and Imines of Phosphorus.* John Wiley & Sons, Inc. :New York, 1993. p. 1–305.
13. Gosney, I., Rowley, A.G., *Organophosphorus Reagents in Organic Synthesis.* Eds Cadogan J.I.G. Academic Press: London, 1979, pp. 17–153.
14. Michaelis, A., Gimborn, H.V. *Ber.* **1894**, *27*, 272.
15. (a) Acsnes, G. *Acta Chem. Scand.* **1961**, *15*, 438;
    (b) Ramirez F., Dershowitz S. *J. Org. Chem.* **1957**, *22*, 41–45.
16. Staudinger, H., Meyer, J. *Helv. Chim. Acta.* **1919**, *2*, 619–624.
17. Staudinger, H., Braunholtz, B.H. *Helv. Chim. Acta.* **1921**, *4*, 897–900.
18. Wittig, G., Rieber, M. *Lieb. Ann. Chem.* **1949**, *562*, 177.
19. Wittig, G., Geissler, G. *Lieb. Ann. Chem.* **1953**, *580*, 44–57.
20. Pommer, H. *Angew. Chem.* **1977**, *89*, 437.
21. Wittig, G. *Pure and Appl. Chem.* **1964**, *9*, 245–254.
22. Wittig, G. *Acc. Chem. Res.* **1974**, *7*, 6–14.
23. Vedejs, E., *Science,* **1980**, *207*, 42–44.
24. Bestmann, H.J. *Angew. chem.* **1977**, *89*, 361–376.
25. Bestmann, H.J., Geismann, C., Zimmermann, R. *Chem. Ber.* **1994**, *127*, 1501–1509.
26. Corey, E.J., Marfat, A., Laguzz, A. *Tetrahedron Lett.* **1981**, *22*, 3339–3342.
27. Trippett, S., Walker, D.M. *J. Chem. Soc.* **1961**, 1266–1272.
28. Seyferth, D., Heeren, J.K., Hughes, W.B. *J. Am. Chem. Soc.* **1965**, *87*, 2847–2854.
29. Schmidbaur, H., Schier, A., Frazao, C.M.F., Muller, G. *J. Am. Chem. Soc.* **1986**, *108*, 976–982.
30. Kaska, W.C. *Coord. Chem. Rev.* **1983**, *48*, 1–58.
31. Cramer, R.E., Jeong, J.H., Richmann, N., Gilje, J. W. *Organometallics,* **1990**, *9*, 1141.
32. Karsch, H.H., Richter, R., Schier, A., Heckel, H., Ficker, R., Hiller, W. *J. Organomet. Chem.* **1995**, *501*, 167.
33. Burton, D.J., Naae, D., Flynn, R.M. *J. Org. Chem.,* **1983**, *48*, 3616.
34. Appel, R., Huppertz, M., Westerhaus, A. *Chem. Ber.* **1983**, *116*, 114–118.
35. Fluck, E., Braun, R. *Phosphorus, Sulfur, and Silicon.* **1989**, *44*, 291–301.
36. Ramires, F., Pilot, I.F., Desai, N.B., Smith, C. *J. Am. Chem. Soc.* **1967**, *89*, 6273–6276.

37.   Corey, E.J., Navasaka, K, Shibasaki, M. *J Am. Chem. Soc.* **1976**, *98*, 6417.

38.   Vedeis, E., Peterson, E. *Top. in Stereochem.* **1994**, *21*, 1–157.

39.   Mari, F., Lahti, M., McEven, W. E. *J. Am. Chem. Soc.,* **1992**, *114*, 813–821.

40.   Streitwisser, A., Rajca, A., MacDawell, R.S., Glaser, R. *J. Am. Chem. Soc.* **1987**, *109*, 4184–4188.

41.   Dixon, D.A., Smart, B.E. *J. Am. Chem. Soc.* **1986**, *108*, 7172–7177.

42.   Bock, H. *Pure and Appl. Chem.* **1975**, *44*, 343–371.

43.   Gilheany, G.G. *Chem. Rev.* **1994**, *94*, 1339. –1374.

44.   Cristau, H. -J. *Chem. Rev.* **1994**, *94*, 1299–1313.

45.   Schmidpeter, A., Noth, H., Jochem, G., Schrodel, H., Karaghiosof, K. *Chem. Ber.* **1995**, *128*, 379–393.

46.   Heim, U., Pritzkow, H., Fleisher, U., Grutzmacher, H., Sanchez, M., Reau, R., Bertrand, G. *Chem. Eur. J.* **1996**, *2*, 68.

47.   Grutzmacher, H., Pritzkow, H. *Angew. Chem.* **1992**, *104*, 92.

48.   Lischka, H. *J. Am. Chem. Soc.* **1977**, *99*, 353–366.

49.   Schlosser, M., Jenny, T., Schaub, B. *Heteroatom. Chem.* **1990**, *1*, 151–156.

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.

$$R_C-\!\!\!\!\overset{\displaystyle R_C}{\underset{\displaystyle R_C}{P}}\!\!\!=C\!\!\!\overset{\displaystyle R_C}{\underset{\displaystyle R_C}{}}$$
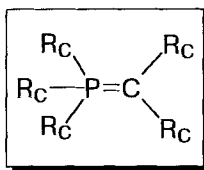
In the earliest days of ylide chemistry almost all P-ylides were C,P-carbon-substituted. Only in recent years has the chemistry of phosphorus ylides of other types, in particular C- and P-heterosubstituted phosphorus ylides, been extensively developed.[1] Depending on the substituents on the carbon atom 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.

$$Ph_3P{=}CR^1R^2 \longleftrightarrow Ph_3\overset{+}{P}{-}\overset{-}{C}R^1R^2$$
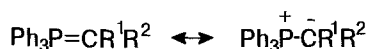
In view of the large variation in their reactivity, C,P-carbon-substituted phosphorus ylides can be classified according to the substituents on the a carbon atom (Scheme 2.1). The simplest representatives of C,P-carbon-substituted phosphorus ylides are *phosphonium methylides* **1**. The replacement 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.**

$$R_3P=CH_2 \qquad R_3P=CHAlk \qquad R_3P=CAlk_2 \qquad R_3P=CHAr$$

| **1** | **2** | **3** | **4** |

$$R_3P=CAr_2 \qquad R_3P=CHCR'=CR'_2$$

5 **6** **7**

$$R_3P=CHC(O)H \qquad R_3P=CHC(O)R' \qquad R_3P=CR'CH \;\;\longleftrightarrow\;\; R_3PCH=CR'$$

8 **9** **10**

| **11** | **12** | **13** |

14 **15** **16**
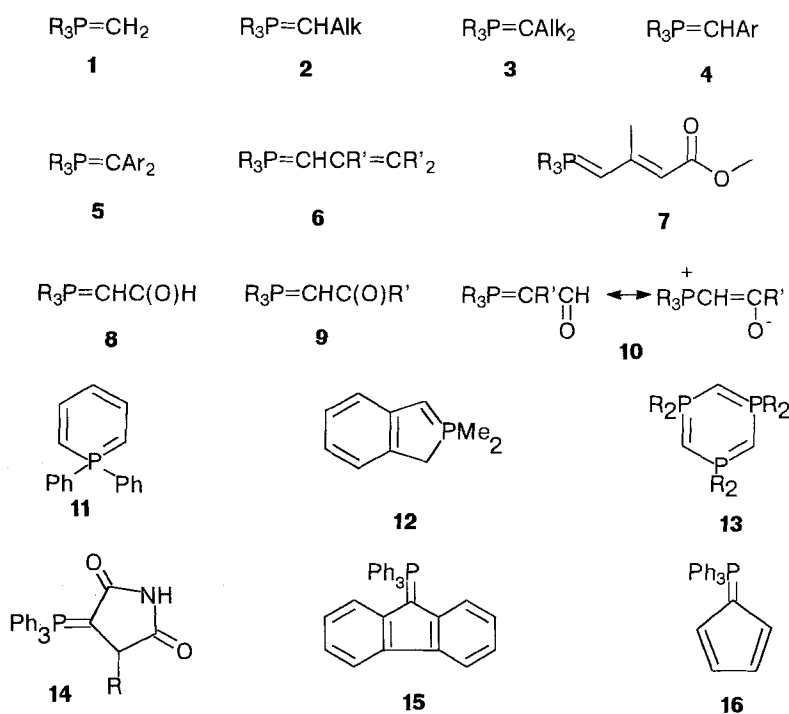
Scheme 2.1

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].

$$Ph_3P^+\text{-}CHRR']X \underset{+HX}{\overset{-HX}{\rightleftharpoons}} Ph_3P=CRR \tag{2.1}$$
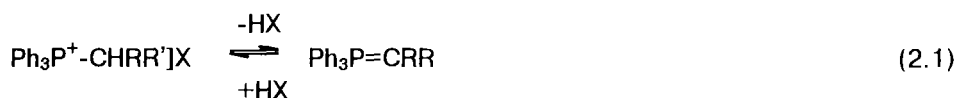
This method can be used to prepare ylides containing different substituents at the ylidic carbon and phosphorus atoms. Various modifications of the salt method are possible (in homogenous and heterogeneous media, on polymeric supports, by electrolysis of the phosphonium salts, by elimination of trimethylchlorosilane 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):

$$R^1_3P \ + \ BrCHR^2R^3 \xrightarrow{\text{Base}} [R^1_3P^+CHR^2R^3]Br^- \xrightarrow{\text{Solvent}} R^1_3P{=}C\,R^2R^3 \qquad (2.2)$$
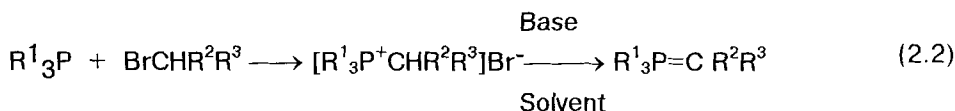
There are general articles which describe in detail various routes of approach to the phosphonium salts, which are now very accessible compounds.[5] Therefore phosphonium salts with various structures, and then phosphorus ylides, can be synthesized by this method.

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	$i\text{-}Pr_2NLi$	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)
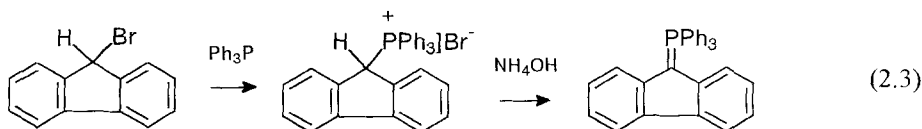
Preparation of triphenylphosphonium fluorenylide (Eq. 2.3) [28]

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 fluorentriphenyl-phosphonium 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]

$$[Ph_3P^+CH_2R]Cl^- \xrightarrow{\text{DBN/DMSO}} Ph_3P=CHR \xrightarrow[-Ph_3PO]{\text{PhCHO}} PhCH=CHR \qquad (2.4)$$
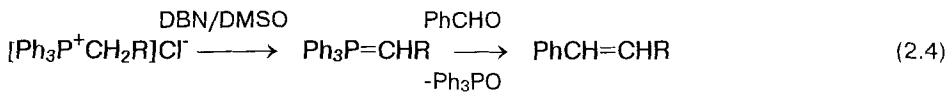
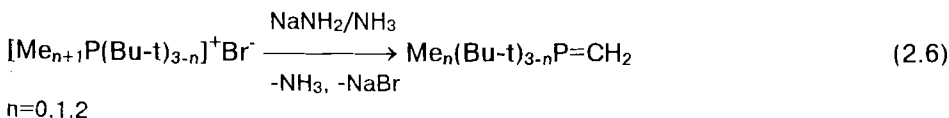R= -C(CH$_3$)=CHCO$_2$Me, CO$_2$CH$_3$

Sodium and potassium amides,[33,34] lithium diethylamide,[35,36] lithium diisopropyl-amide,[37] lithium piperidide,[38] lithium, potassium and sodium bis(trimethylsilyl) amides[39,40] are used more often than alkylamines and ammonia for the dehydro-halogenation 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]

$$[Ph_3P^+CH_2Et]Br^- \xrightarrow[-NaBr]{NaN(SiMe_3)_2} Ph_3P=CHEt \qquad\qquad (2.5)$$
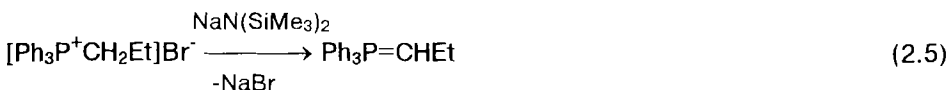
The deprotonation of phosphonium salts with sodium amide can be performed in liquid ammonia, in which it was prepared directly, or in organic solvents with previously prepared, solid, sodium amide. Sodium amide can also be used in the form of a suspension in mineral oil—powdered sodium amide coated with 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-butyl-dimethylphosphonium 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]:

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

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).

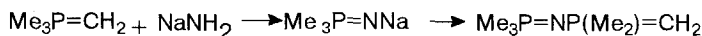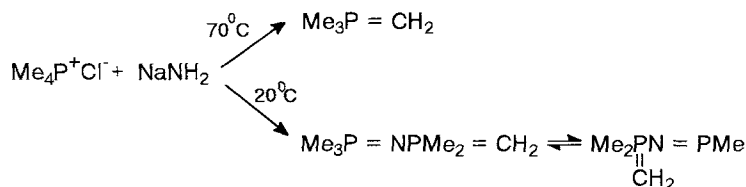A useful perfection of the salt method are the *instant ylidic mixtures* proposed by Schlosser and Schaub[43–47]. The instant ylide method relies on the surprising inertness of sodium amide (pK_a ammonia ~40) towards phosphonium salts (pK_a ~20) as long as the two components are mixed in the form of 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 alkyltriphenyl-
phosphonium salts are ready to use and are well preserved in a closed flask (6 months
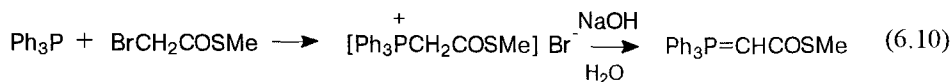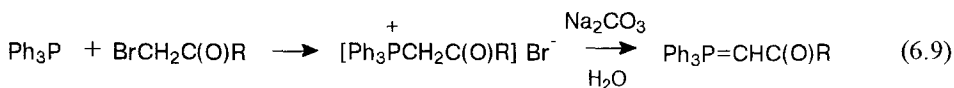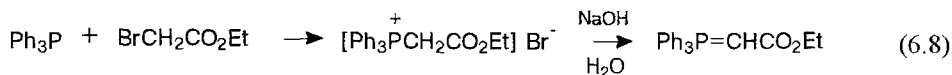at 0°C). The preparation of these mixtures can be easily performed on ordinary
balances.

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

R=Me, CH2F, CH2OMe, NC5H4CH2CH2. X=Br, Cl, BF4   (2.7)
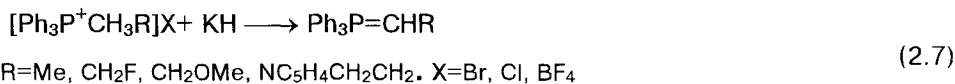
Instant ylidic mixtures are very convenient for the olefination of carbonyl compounds
in the Wittig reaction (Chapter 6, Section 6.2.1).[43–47]
Sometimes the reaction of phosphonium salts with sodium amide is accompanied with
complications.[33] For example, the dehydrochlorination of tetramethylphosphonium
chloride with sodium amide in boiled tetrahydrofuran proceeds smoothly to result in
trimethylphosphonium methylide (Scheme 2.2).

$$Me_4P^+Cl^- + \ NaNH_2 \ \begin{array}{c} \nearrow ^{70^0C} \ Me_3P = CH_2 \\ \searrow _{20^0C} \ Me_3P = NPMe_2 = CH_2 \ \rightleftharpoons \ Me_2PN = PMe \\ \underset{CH_2}{\overset{\|}{}} \end{array}$$

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

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]

$$Ph_3P \ + \ BrCH_2CO_2Et \ \longrightarrow \ [Ph_3PCH_2CO_2Et] \ Br^- \ \overset{NaOH}{\underset{H_2O}{\longrightarrow}} \ Ph_3P=CHCO_2Et \qquad (6.8)$$

$$Ph_3P \ + \ BrCH_2C(O)R \ \longrightarrow \ [Ph_3PCH_2C(O)R] \ Br^- \ \overset{Na_2CO_3}{\underset{H_2O}{\longrightarrow}} \ Ph_3P=CHC(O)R \qquad (6.9)$$

$$Ph_3P \ + \ BrCH_2COSMe \ \longrightarrow \ [Ph_3PCH_2COSMe] \ Br^- \ \overset{NaOH}{\underset{H_2O}{\longrightarrow}} \ Ph_3P=CHCOSMe \qquad (6.10)$$

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