Takeshi Takeda (Ed.)

Modern Carbonyl Olefination

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Contents

Preface

This book summarizes the recent progress in the major methodologies of carbonyl olefination, which is one of the most fundamental transformations in organic synthesis. Carbonyl olefination has been extensively studied since Professor Georg Wittig discovered in 1953 the reaction of phosphonium ylides with carbonyl compounds, which has become known as the Wittig reaction. Since then, a variety of reagents have been developed for this transformation by a number of chemists. These reagents enable us to transform various carbonyl functions into carbon-carbon double bonds with different chemo- and stereoselectivities and are utilized in a variety of organic syntheses.

The mechanisms of these reactions bear marked similarities, in spite of the differences in their reactivities and selectivities. Thus, in certain cases, a four-membered intermediate similar to the 1,2-oxaphosphetane intermediate in the Wittig reaction appears in the Peterson reaction as a pentacoordinate 1,2-oxasiletanide. Reactions of transition metal carbene complexes with carbonyl compounds also proceed through the formation of a four-membered oxametallacycle, which was recently found to be an intermediate of some McMurry reactions. Carbonyl olefination utilizing dimetallic species of zinc or chromium is somewhat similar to the Julia reaction in that they both involve the process of β-elimination.

In this book, an effort has been made to provide comprehensive yet concise commentaries on the mechanisms of each reaction, as well as on their synthetic applications. These provide an accurate prescription for their use and should be useful for the development of a broader perspective on carbonyl olefination. The final chapter is concerned with asymmetric carbonyl olefination, which is one of the frontiers of organic synthesis. As this subject exemplifies, the established methodologies are not necessarily perfect and there still remain many problems to be solved in the field of carbonyl olefination. It is hoped that this book will be of wide use to all chemists engaged in organic synthesis, both in industrial laboratories and in academic institutions.

I would like to thank the authors of the individual chapters for their excellent contributions. This volume was only possible with the cooperation of the authors, who are experts in each field. Finally, I express my sincere gratitude to my wife, Yukiko, whose continuous encouragement was essential to the editing of this book.

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Tokyo, 2003

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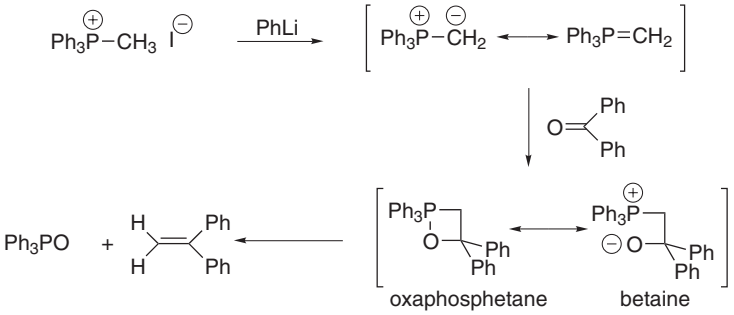
1
The Wittig Reaction

Michael Edmonds and Andrew Abell

1.1
Introduction

The reaction of a phosphorus ylide with an aldehyde or ketone, as first described in 1953 by Wittig and Geissler [1] (see Scheme 1.1), is probably the most widely recognized method for carbonyl olefination.



Scheme 1.1. The Wittig reaction.

This so-called Wittig reaction has a number of advantages over other olefination methods; in particular, it occurs with total positional selectivity (that is, an alkene always directly replaces a carbonyl group). By comparison, a number of other carbonyl olefination reactions often occur with double-bond rearrangement. In addition, the factors that influence *E*- and *Z*-stereoselectivity are well understood and can be readily controlled through careful selection of the phosphorus reagent and reaction conditions. A wide variety of phosphorus reagents are known to participate in Wittig reactions and the exact nature of these species is commonly used to divide the Wittig reaction into three main groups, namely the ''classic'' Wittig reaction of phosphonium ylides, the Horner–Wadsworth–Emmons reaction of phosphonate anions, and the Horner–Wittig reaction of phosphine oxide anions. Each of these reaction types has its own distinct advantages and limitations, and

these must be taken into account when selecting the appropriate method for a desired synthesis.

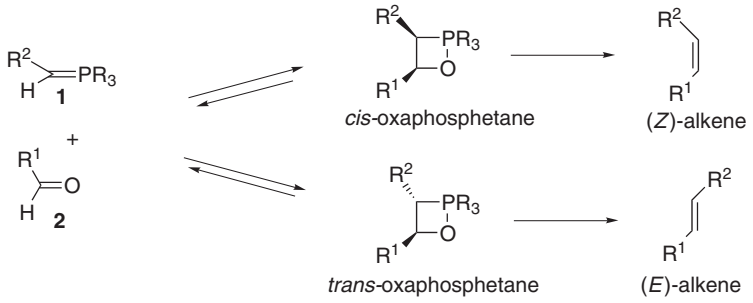
1.2
The "Classic" Wittig Reaction [1–4]

The original work of Wittig and Geissler [1], as depicted in Scheme 1.1, provides a good example of a classic Wittig reaction in which a phosphonium ylide reacts with an aldehyde or ketone to afford the corresponding alkene and phosphine oxide. This reaction is very general and provides a convenient method for the preparation of a range of alkenes with good stereocontrol. The starting phosphonium ylides are themselves readily generated by the addition of a suitable base to the corresponding phosphonium salt (refer to Section 1.2.3).

1.2.1
Mechanism and Stereoselectivity

The mechanism of the Wittig reaction has long been considered to involve two intermediate species, a diionic betaine and an oxaphosphetane, as shown in Scheme 1.1. However, there has been much debate as to which of these two species plays the most important mechanistic role and also as to how each influences the stereochemical outcome under different reaction conditions. For many years, it was generally accepted that the betaine is the more important intermediate [5, 6]; however, recent low temperature ^{31}P NMR studies suggest that this may not be the case [7, 8]. This supposition is further supported by recent calculations that reveal that oxaphosphetanes are of lower energy than the corresponding betaines [9]. As such, the currently accepted mechanism for the Wittig reaction is as shown in Scheme 1.2 [4]. For a more detailed account of the evolution of the Wittig mechanism, the reader is referred to the excellent reviews by Vedejs and co-workers [4, 10].

The stereoselectivity of the Wittig reaction is directly linked to this mechanism. In particular, the reaction of a carbonyl compound with an ylide produces both the



Scheme 1.2. The mechanism of the Wittig reaction.

cis and *trans* oxaphosphetanes (Scheme 1.2), which undergo stereospecific syn-elimination to give the corresponding *E*- and *Z*-alkenes, respectively. The *Z*-alkene tends to predominate under kinetic conditions, indicating an intrinsic preference for the *cis*-oxaphosphetane, a preference that as yet is not fully understood. However, under thermodynamic conditions, equilibration of the two oxaphosphetanes with reactants **1** and **2** allows predominant formation of the more stable *trans*-oxaphosphetane and hence the *E*-alkene. This is supported by reaction rate studies, which show that *cis*-oxaphosphetanes undergo retro-Wittig decomposition much faster than their *trans* counterparts [11–13]. It should be noted that the extent of the retro-Wittig decomposition is dependent on both the nature of the substituent on the oxaphosphetane and the reaction conditions used. A number of factors determine whether a Wittig reaction is under kinetic or thermodynamic control, one of the most important and readily controllable being the type of ylide used.

1.2.2
Nature of the Ylide and Carbonyl Compound

Stabilized ylides are those that possess an R substituent (Figure 1.1) that is anion-stabilizing/electron-withdrawing (e.g. CO_2CH_3, CN). Such ylides tend to be less reactive than other ylides and usually only react with aldehydes to give the *E*-alkene. This *E*-selectivity has been attributed to the fact that stabilized ylides react with aldehydes under thermodynamic control. Consequently, the less crowded and hence favored *trans*-oxaphosphetane gives rise to the observed *E*-alkene. Other factors that influence the *E*/*Z* ratio of alkenes in reactions of a stabilized ylide with an aldehyde are listed in Table 1.1.

In contrast, non-stabilized ylides possess an R substituent (Figure 1.1) that is anion-destabilizing/electron-releasing (e.g. alkyl groups). Reactions of these ylides with an aldehyde or ketone are generally under kinetic control and as a consequence give the *Z*-alkene. A number of factors influence the *E*/*Z* ratio of alkenes in reactions of non-stabilized ylides, and these are listed in Table 1.1.

The addition of a second equivalent of a strong base, usually an alkyllithium, to reactions of non-stabilized ylides facilitates the formation of the *E*-alkene (Scheme 1.3). The resulting *β*-oxido ylide is then quenched with acid under kinetic control to afford the *E*-alkene. This sequence is known as the Schlosser modification [14–16]. Lithium bases must be employed here since the presence of lithium ions is required to convert the oxaphosphetane **3** into the more acidic betaine.

The nature of the reactant carbonyl group in the substrate also influences the stereoselectivity of the Wittig reactions; for example, primary aliphatic aldehydes

Triphenylphosphorane ylides are readily accessible by the reaction of triphenylphosphine with a suitable halide (See Section 1.2.3)

Fig. 1.1. R-Substituted ylides.

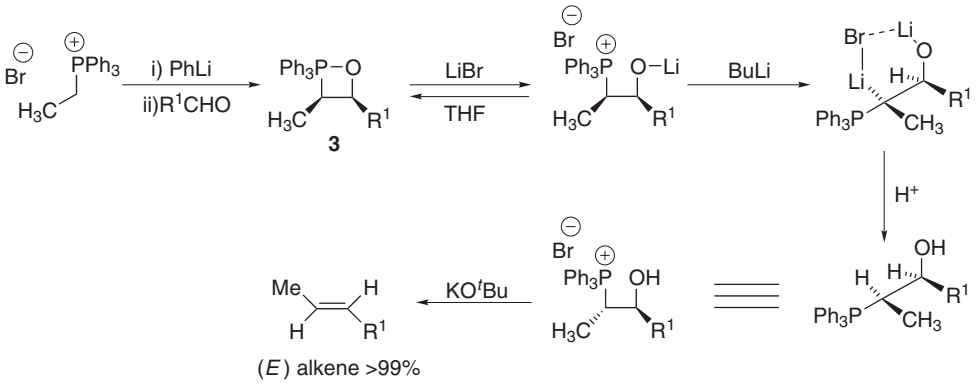
Tab. 1.1. Factors that influence the *E*/*Z* ratio in the "classic" Wittig reaction.

Stabilized Ylides	
Factors that favor the E-alkene	***Factors that disfavor the E-alkene***
Aprotic conditions A catalyic amount of benzoic acid[62]	Li and Mg salts in DMF as solvent Use of α-oxygenated aldehydes or methanol as solvent
Non-stabilized Ylides	
Factors that favor the Z-alkene	***Factors that disfavor the Z-alkene***
Bulky and/or aliphatic aldehydes Bulky phosphorus ligands, e.g. phenyl ligands Lithium-free conditions/lower temperatures Hindered ylides Low temperature	Small phosphorus ligands, cyclohexyl ligands Cyclic phosphorus ligands Aromatic or α,β-unsaturated aldehydes Use of Schlosser modification

favor *Z*-alkenes, while aromatic or α,β-unsaturated aldehydes tend to reduce *Z*-selectivity, especially in polar aprotic solvents. In addition, aryl alkyl ketones tend to give a higher *Z*-selectivity as compared to unsymmetrical dialkyl ketones.

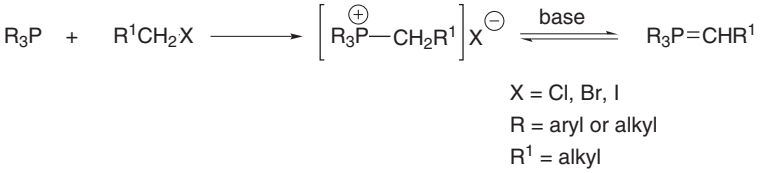
1.2.3 Reagents and Reaction Conditions

Phosphonium ylides are typically prepared by the reaction of a phosphonium salt with a base. Non-stabilized ylides require a strong base (such as BuLi) under inert conditions, while stabilized ylides require a weaker base (for example, alkali metal hydroxides in aqueous solution). For more detail on the variety of bases and reaction conditions that can be used in the Wittig reaction, see references [2] and [5].



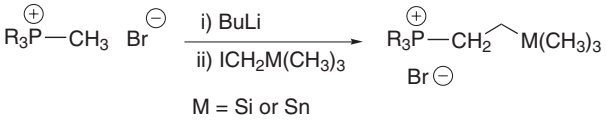
Scheme 1.3. The Schlosser modification.

The starting phosphonium salts are themselves readily obtained by reaction of triaryl- or trialkylphosphines with an alkyl halide (Scheme 1.4). In general, primary alkyl iodides and benzyl bromides are converted to the corresponding phosphonium salts by heating with triphenylphosphine at 50 °C in THF or $CHCl_3$, while primary alkyl bromides, chlorides, and branched halides usually require more vigorous conditions (for example, heating to 150 °C). These reactions can be carried out neat, or in acetic acid, ethyl acetate, acetonitrile or DMF solution.



Scheme 1.4. Preparation of phosphonium salts.

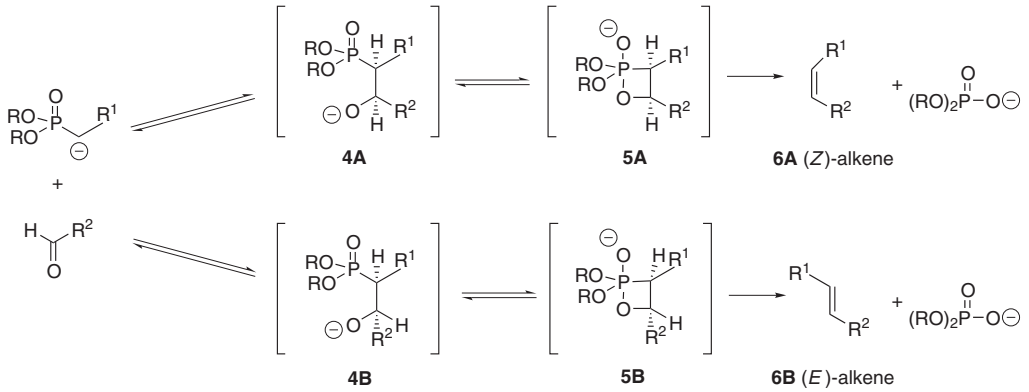
Phosphonium salts can also be prepared by alkylating existing phosphonium salts. This method has been used to incorporate interesting groups, such as silyl and stannyl functionalities [17, 18] (Scheme 1.5), into phosphonium salts. Such salts, upon reaction with base and aldehyde, produce synthetically useful allylsilanes and -stannanes.



Scheme 1.5. Alkylation of phosphonium salts.

1.3
Horner–Wadsworth–Emmons Reaction [2, 3, 19]

The reaction of a phosphonate-stabilized carbanion with a carbonyl compound is referred to as the Horner–Wadsworth–Emmons reaction (HWE); see Scheme 1.6. The phosphonates used here are significantly more reactive than classical Wittig stabilized ylides and as such react with ketones and aldehydes. Another advantage of the HWE reaction over the classic Wittig reaction is that the phosphorus by-products are water-soluble and hence readily separated from the desired product. Phosphonates that lack a stabilizing α-substituent at R^2 (for example COO^-, COOR, CN, SO_2R, vinyl, aryl $P(O)(OR)_2$, OR or NR_2) generally result in a low yield of the product alkene. The starting phosphonates are readily prepared by means of the Arbuzov reaction of trialkyl phosphites with an organic halide (Section 1.3.2).



Scheme 1.6. The Horner–Wadsworth–Emmons reaction.

1.3.1
Mechanism and Stereochemistry

The commonly accepted mechanism for the Horner–Wadsworth–Emmons reaction is as depicted in Scheme 1.6. Here, reaction of the phosphonate stabilized carbanion with an aldehyde forms the oxyanion intermediates **4** under reversible conditions. Rapid decomposition of **4**, via the four-centered intermediates **5**, then affords alkenes **6**.

The stereochemical outcome of the Horner–Wadsworth–Emmons reaction is primarily dependent on the nature of the phosphonate used. In general, bulky substituents at both the phosphorus and the carbon adjacent to the carbanion favor formation of the *E*-alkene. This selectivity has been rationalized in terms of a lowering of steric strain in intermediate **5B** as compared to intermediate **5A**. *Z*-Selectivity in HWE reactions can, however, be achieved using the Still–Gennari modification [20]. Here, the use of a (2,2,2-trifluoroethyl) phosphonate enhances the rate of elimination of the originally formed adduct **5A** (Scheme 1.6) relative to equilibration of the intermediates **4** and **5**. An example of the Still–Gennari modification is illustrated in Scheme 1.7.

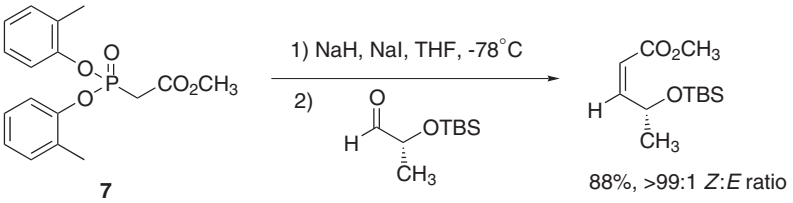
The so-called Ando method [21, 22] also provides access to a *Z*-alkene, as illustrated in Scheme 1.8 [23], where >99% *Z*-selectivity was obtained using

Reaction conditions

a) $(EtO)_2POCH_2CO_2Et$, NaH, THF — 83%, *E*:*Z* = 12:1

b) $(CF_3CH_2O)_2POCH_2CO_2CH_3$, KH, THF — 84% *E*:*Z* = 1:11

Scheme 1.7. The Still–Gennari modification.



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Scheme 1.8. The Ando method.

Ando's bis(*o*-methylphenyl) phosphonoacetate **7** in the presence of excess Na^+ ions (Scheme 1.8).

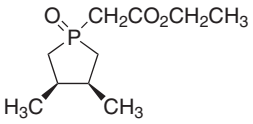
Some common factors that influence the stereochemical outcome of the HWE reaction are summarized in Table 1.2. In general, the addition of a phosphonate to a ketone occurs with moderate *E*-selectivity [24]. The reaction of an α-substituted phosphonate with an aldehyde also usually favors the *E*-alkene (Scheme 1.9), although some exceptions have been noted [25, 26]. The *E*-selectivity is further enhanced with the use of large phosphoryl and carbanion substituents [27, 28]. However, α-substituted phosphonates that bear a large alkyl chain give only modest *E*-selectivity. α-Fluoro phosphonates are reported to provide impressive *E*- or *Z*-stereoselectivity (Scheme 1.10), which has been attributed to electronic effects [29].

Substituents on the carbonyl compound can also influence the stereo-outcome of the HWE reaction. For example, carbonyl compounds that possess oxygenated groups at the α- or β-position generally favor the *E*-alkene [30, 31], although some exceptions have been observed [32].

The synthesis of tetrasubstituted alkenes using the HWE reaction generally proceeds with moderate selectivity [33, 34].

Tab. 1.2. Factors that influence the ratio *E*/*Z* alkenes in the Horner–Wadsworth–Emmons reaction.

Factors that favor the E-alkene	*Factors that favor the Z-alkene*
Bulky R groups on the phosphonate e.g. $(RO)_2P(O)–CH(–)–R$	Use of bis(2,2,2-trifluoroethyl) phosphonates (Still–Gennari modification)
Bulky R′ groups adjacent to the carbanion e.g. $(RO)_2P(O)–CH(–)–R'$	Use of cyclic phosphonates such as **8**
Use of α-fluoro phosphonates	Use of (diarylphosphono)acetates (Ando method)/ excess Na^+ ions



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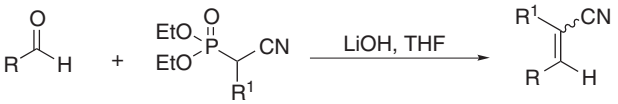
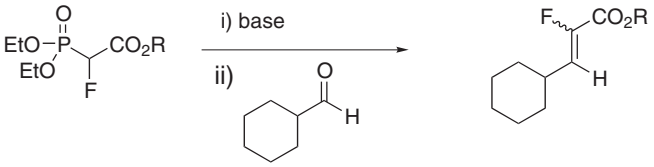


R	R^1	*E*/*Z*, yield
Ph	H	90:10, 70%
Ph	CH_3	77:23, 85%
nC_7H_{15}	H	68:32, 74%
nC_7H_{15}	CH_3	58:42, 72%

Scheme 1.9. The effect of α-substituted phosphonate on *E*/*Z* ratio in the Horner–Wadsworth–Emmons reaction.

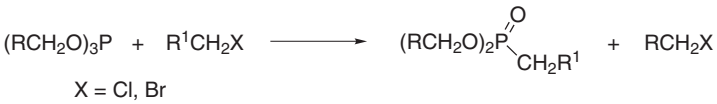


R	Base	*E*/*Z*, yield
Et	*n*BuLi	94:6, 83%
H	*i*PrMgBr	>1:99, 84%

Scheme 1.10. High stereoselectivity using α-fluorinated phosphonates in the Horner–Wadsworth–Emmons reaction.

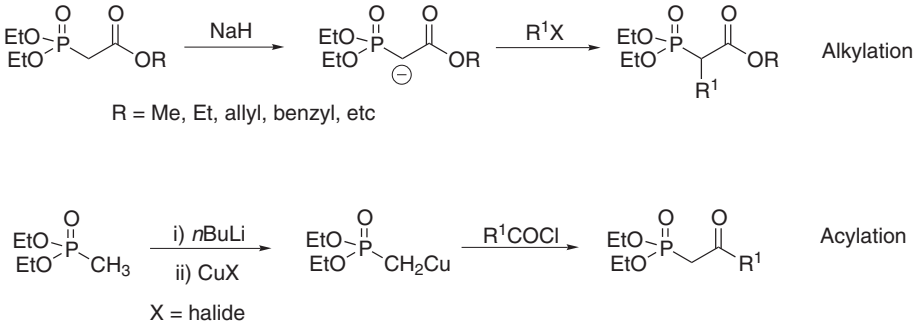
1.3.2
Reagents and Reaction Conditions

The starting phosphonates are readily obtained by the Michaelis–Arbuzov reaction of trialkyl phosphites with an organic halide, and as would be expected, alkyl bromides are more reactive than the corresponding chlorides (Scheme 1.11).



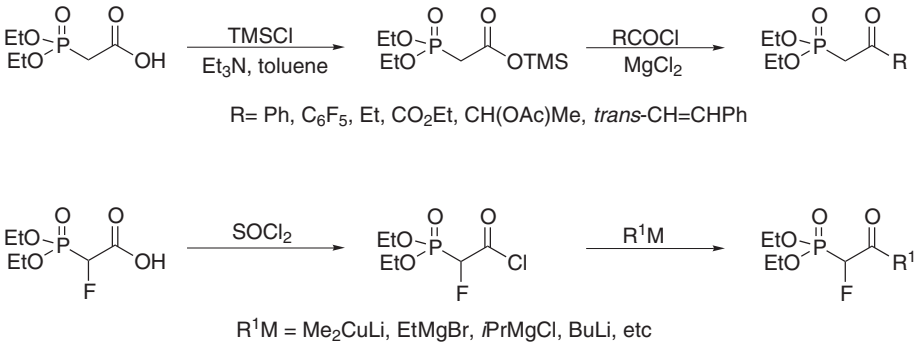
Scheme 1.11. The Michaelis–Arbuzov reaction.

An existing phosphonate can be further elaborated by alkylation or acylation of the phosphonate carbanion [35, 36] (Scheme 1.12). This provides a useful method for the preparation of β-keto phosphonates that are not generally available by means of the Michaelis–Arbuzov method. A range of β-keto phosphonates is also



Scheme 1.12. Modification of phosphonates by alkylation and acylation.

readily accessible through the acylation of TMS esters [37] or acid chlorides of dialkyl phosphonoacetic acids [38] (Scheme 1.13).



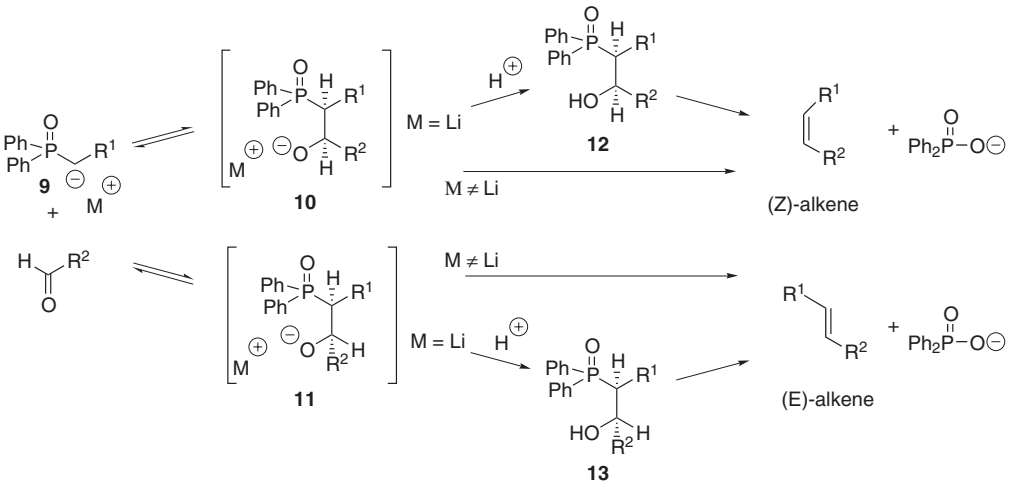
Scheme 1.13. Preparation of β-ketophosphonates using TMS esters and acid chlorides.

As stated above, phosphonates react with both aldehydes and ketones, although ketones generally require more vigorous conditions. Long chain aliphatic aldehydes tend to be unreactive, while readily enolizable ketones usually give poor yields of the alkene.

A wide variety of bases and reaction conditions have been successfully applied to the HWE reaction, including phase-transfer catalysis.

1.4 Horner–Wittig (HW) Reaction [2, 3, 39]

Horner and co-workers were the first to describe the preparation of an alkene by treatment of a phosphine oxide with base followed by the addition of an aldehyde (Scheme 1.14) [40–42]. While initial experiments using bases such as potassium *tert*-butoxide produced the alkenes directly, it was quickly realized that the use of lithium bases allowed the intermediate β-hydroxy phosphine oxide diastereomers to be isolated and separated [40]. Each diastereomer can then be separately treated



Scheme 1.14. The Horner–Wittig reaction.

with base to give the corresponding alkenes with high geometrical purity (Scheme 1.14).

Like the HWE reaction, the HW reaction gives rise to a phosphinate by-product that is water-soluble and hence readily removed from the desired alkene.

1.4.1 Mechanism and Stereochemistry

As mentioned above, the use of lithium bases in the HW reaction allows the reaction to be divided into two discrete steps [39]: 1) the ***HW addition*** of a lithiated phosphine oxide to an aldehyde (or ketone) to produce a *β*-hydroxy phosphine oxide, and 2) the ***HW elimination*** of a phosphinic acid to afford an alkene (Scheme 1.14). Careful manipulation of each step then allows control of the overall sequence. While the overall mechanism of the Horner–Wittig reaction is similar to that of the HWE reaction (Scheme 1.6), some additional discussion is required to understand its stereochemical outcome. The HW reaction can be carried out without isolation of the intermediate *β*-hydroxy phosphine oxides in cases where a non-lithium base is used and R^1 is able to stabilize the negative charge of the phosphorus *α*-carbanion **9**. Under these conditions, reaction of an aldehyde with the phosphine oxide to give intermediates **10** and **11** is reversible. The *E*-alkene is then formed preferentially since elimination of intermediate **11** occurs much faster than that of **10**.

However, if a lithium base is used and the reaction is carried out at low temperature, the intermediate *β*-hydroxy phosphine oxides **12** and **13** can be isolated (Scheme 1.14). Under these conditions, the *erythro* intermediate **12** predominates and this then undergoes *syn*-elimination to give the *Z*-alkene.

In cases where R^1 is unable to exert a stabilizing effect and a lithium base is used, the intermediates **10** and **11** do not undergo elimination and instead *β*-

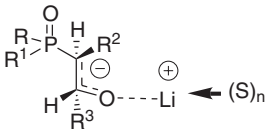


Fig. 1.2. Solvent-stabilized transition state model for the Horner–Wittig reaction.

hydroxy phosphine oxides **12** and **13** are readily isolated. These diastereomeric intermediates can then be separated by column chromatography or crystallization. When R^1 is non-stabilizing, HW addition reactions generally display limited stereocontrol, although under certain conditions (bulky R groups on the phosphine oxide and aldehyde; polar solvents) high *Z*-selectivity can be effected. It has been proposed that under these conditions the favored transition state has the solvent-stabilized oxido group positioned *anti* to the bulky phosphinyl group (Figure 1.2) [3].

Clayden and Warren have proposed the transition state model depicted in Figure 1.3 to explain the stereoselectivity observed for the HW reaction of a range of phosphine oxides, as summarized in Table 1.3 [39].

According to this model, both R^1 and R^2 occupy the less sterically demanding *exo* positions to give preferential formation of the *Z*-product. However, as the bulk of the R^1 group increases, the effect of steric interactions between R^1 and R^2, and R^1 and the *exo* Ph–P ring, is to make the R^1 group occupy the pseudo-equatorial *endo* position, thereby lowering the *Z*-selectivity (see Table 1.3). For moderately sized R^2 groups, the *exo* position (Figure 1.3) is favored since the *endo* position suffers from 1,3-diaxial interactions with the *endo* Ph–P ring. However, if R^1 is very small (e.g. Me), the lesser 1,3-diaxial interactions will reduce the *Z*-selectivity. Furthermore, if R^2 is large, its steric interaction with R^1 also reduces the *Z*-selectivity. The model depicted in Figure 1.3 suggests that the use of ketones or di-α-substituted phosphine oxides in the HW reaction would produce very little stereoselection. This is usually true unless there is a substantial difference in size between the two substituents on the ketone or di-α-substituted phosphine oxide. One such example is illustrated in Scheme 1.15 [43].

The presence of R^1 groups capable of coordinating to lithium (e.g. OMe, NR_3) also lowers the *Z*-selectivity, presumably by altering the structure of the transition state complex. Indeed, in at least one case (last entry of Table 1.3), significant *E*-selectivity is observed [44].

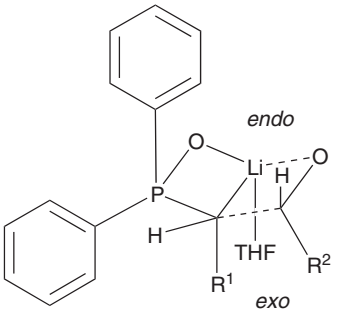
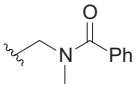
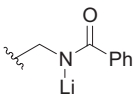
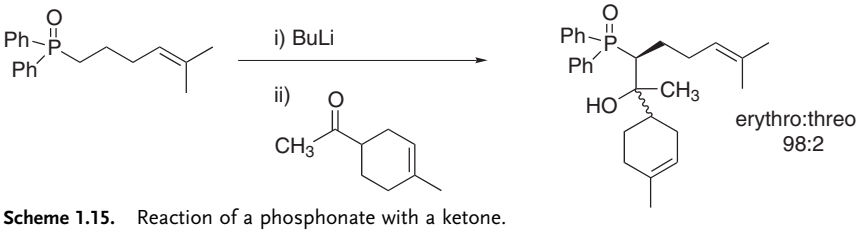


Fig. 1.3. Transition state model for the Horner–Wittig reaction.

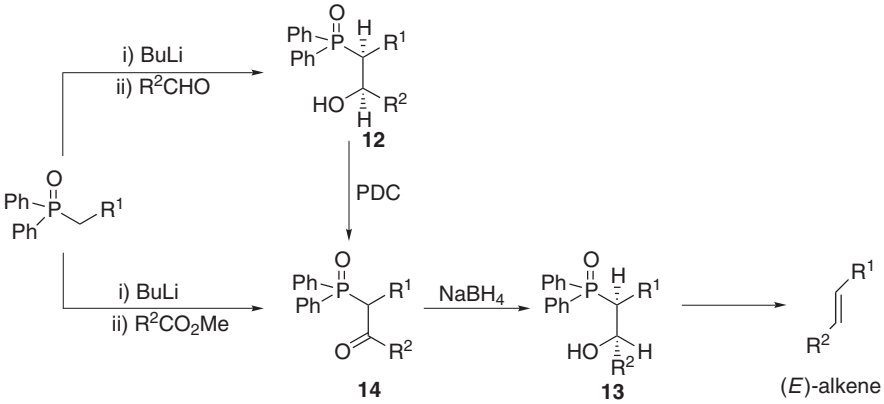
Tab. 1.3. The effect of phosphonate and aldehyde substitution on *Z*/*E* stereoselectivity.

R^1	R^2	Yield (%)	Z/E ratio
Me	Ph	88	88:12
Bu	Ph	84	84:16
^{i}Bu	Ph	81	80:20
Ph	Ph	88	83:17
Me	cyclohexyl	86	79:21
Me	Me	93	75:25
Ph	Me	97	72:28
^{i}Pr	Pr	84	57:43
cyclohexyl	Pr	100	53:47
OMe	C_6H_{13}	79	50:50
	Me	68	55:45
	Ph	80	5:95



Scheme 1.15. Reaction of a phosphonate with a ketone.

Since high *E*-selectivity is usually not possible using phosphine oxides that bear a non-stabilizing R group, the *threo* intermediate (and hence the *E*-alkene) must be obtained indirectly. Such an approach has been developed by Warren et al. (Scheme 1.16) [45, 46]. Oxidation of the 1,2-phosphinoyl alcohol **12** or acylation of



Scheme 1.16. Warren's method for indirect access to *E*-alkenes.