

Takeshi Takeda (Ed.)

Modern Carbonyl Olefination



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**Modern Carbonyl
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Library of Congress Card No.: applied for

A catalogue record for this book is available from the British Library.

Bibliographic information published by Die Deutsche Bibliothek

Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>

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Printed in the Federal Republic of Germany.

Printed on acid-free paper.

Typesetting Asco Typesetters, Hong Kong

Printing Strauss Offsetdruck GmbH, Mörlenbach

Bookbinding J. Schäffer GmbH & Co. KG, Grünstadt

ISBN 3-527-30634-X

Contents

Preface *xiii*

List of Authors *xv*

1	The Wittig Reaction	1
	<i>Michael Edmonds and Andrew Abell</i>	
1.1	Introduction	1
1.2	The “Classic” Wittig Reaction	2
1.2.1	Mechanism and Stereoselectivity	2
1.2.2	Nature of the Ylide and Carbonyl Compound	3
1.2.3	Reagents and Reaction Conditions	4
1.3	Horner–Wadsworth–Emmons Reaction	5
1.3.1	Mechanism and Stereochemistry	6
1.3.2	Reagents and Reaction Conditions	8
1.4	Horner–Wittig (HW) Reaction	9
1.4.1	Mechanism and Stereochemistry	9
1.4.2	Reagents and Reaction Conditions	14
1.5	Conclusion	15
	References	16
2	The Peterson and Related Reactions	18
	<i>Naokazu Kano and Takayuki Kawashima</i>	
2.1	Introduction	18
2.2	Stereochemistry and the Reaction Mechanism of the Peterson Reaction	19
2.2.1	Stereochemistry and the Reaction Mechanism of the Peterson Reaction of β -Hydroxyalkylsilanes	19
2.2.1.1	Stepwise Mechanism	21
2.2.1.2	Reaction Mechanism via a 1,2-Oxasiletanide	22
2.2.2	Reaction Mechanism of the Addition Step of an α -Silyl Carbanion to a Carbonyl Compound	23
2.2.2.1	Approach Control of the Transition State	23
2.2.2.2	Concerted Mechanism	25
2.2.2.3	Chelation Control Mechanism	26

2.2.3	Theoretical Calculations on the Reaction Mechanism	29
2.2.4	Convergently Stereoselective Peterson Reactions	31
2.3	Generation of α -Silyl Carbanions and their Peterson Reactions	32
2.3.1	Generation of α -Silyl Carbanions from α -Silylalkyl Halides	32
2.3.1.1	Generation of α -Silyl Grignard Reagents from α -Silylalkyl Halides	32
2.3.1.2	Generation of α -Silyl Alkylolithium Reagents from α -Silylalkyl Halides	32
2.3.1.3	Synthesis of Terminal Alkenes by the Use of α -Silyl Carbanions Generated from α -Silylalkyl Halides	33
2.3.1.4	Reactions of α -Silyl Carbanions Generated from α -Silylalkyl Halides with Esters, Carboxylic Acids, and Acetals	35
2.3.1.5	The Reformatsky–Peterson Reactions of α -Silylalkyl Halides	37
2.3.2	Generation of α -Silyl Carbanions by Deprotonation of Alkylsilanes	37
2.3.2.1	Generation of α -Silyl Carbanions Bearing an Aryl or a Heteroaryl Group	37
2.3.2.2	Generation of α -Silyl Carbanions Bearing an Alkoxy Group	39
2.3.2.3	Generation of α -Silyl Carbanions Bearing a Nitrogen-Containing Group	41
2.3.2.4	Generation of α -Silyl Carbanions Bearing a Sulfur-Containing Group	41
2.3.2.5	Generation of α -Silyl Carbanions Bearing a Phosphorus-Containing Group	48
2.3.2.6	Generation of α -Silyl Carbanions Bearing a Halogen Group	50
2.3.2.7	Generation of α -Silyl Carbanions from α -Silyl Ketones	52
2.3.2.8	Generation of α -Silyl Carbanions Bearing an Ester Group	52
2.3.2.9	Generation of α -Silyl Carbanions Bearing a Lactone Group	53
2.3.2.10	Generation of α -Silyl Carbanions Bearing Thiocarboxylate or Dithiocarboxylate Ester Groups	53
2.3.2.11	Generation of α -Silyl Carbanions Bearing an Imine Group	53
2.3.2.12	Generation of α -Silyl Carbanions Bearing an Amide Group	54
2.3.2.13	Generation of α -Silyl Carbanions Bearing a Cyanide Group	55
2.3.2.14	Generation of α -Silyl Carbanions from Allylsilanes	56
2.3.2.15	Generation of α -Silyl Carbanions from Propargylsilanes	58
2.3.3	Generation of α -Silyl Carbanions by Substitution of a Heteroatom	58
2.3.3.1	Generation of α -Silyl Carbanions by Reduction of a Sulfanyl Group	58
2.3.3.2	Generation of α -Silyl Carbanions by Substitution of Selenium	59
2.3.3.3	Generation of α -Silyl Carbanions by Desilylation of Bis(trimethylsilyl)methane Derivatives	60
2.3.3.4	Generation of α -Silyl Carbanions by Tin–Lithium Transmetalation	60
2.3.4	Formation of β -Hydroxyalkylsilanes from Silyl Enol Ethers	60
2.3.5	Fluoride Ion Induced Peterson-Type Reactions	62
2.3.5.1	Generation of α -Silyl Carbanions by Fluoride Ion Induced Desilylation	62
2.3.5.2	Fluoride Ion Induced Peterson-Type Reactions of Bis(trimethylsilyl)methane Derivatives	64

2.3.5.3	Fluoride Ion Catalyzed Peterson-Type Reactions of Bis(trimethylsilyl)methylamine Derivatives	65
2.3.5.4	Fluoride Ion Catalyzed Peterson-Type Reactions with Elimination of Trimethylsilanol	68
2.3.6	Generation of α -Silyl Carbanions by Addition of Nucleophiles to Vinylsilanes	68
2.4	Synthetic Methods for β -Silyl Alkoxides and β -Hydroxyalkylsilanes	70
2.4.1	Reactions of α -Silyl Ketones, Esters, and Carboxylic Acids with Nucleophiles	70
2.4.2	Ring-Opening Reactions	72
2.4.2.1	Ring-Opening Reactions of Oxiranes	72
2.4.2.2	Ring-Opening Reactions of Cyclic Esters and Ethers	73
2.4.3	Hydroboration of 1-Silylallenes	74
2.4.4	Dihydroxylation of Vinylsilanes and Allylsilanes	76
2.5	Related Reactions	77
2.5.1	The Homo-Brook Rearrangement	77
2.5.2	Homo-Peterson Reaction	79
2.5.3	Vinylogous Peterson Olefination	80
2.5.4	Tandem Reactions and One-Pot Processes Involving the Peterson Reaction	81
2.5.5	The Germanium, Tin, and Lead Versions of the Peterson Reaction	85
2.5.5.1	The Germanium-Peterson Reaction	85
2.5.5.2	The Tin-Peterson Reaction	86
2.5.5.3	The Lead-Peterson Reaction	88
2.5.6	Synthesis of Carbon–Heteroatom Double-Bond Compounds by Peterson-Type Reactions	88
2.5.6.1	Synthesis of Imines	88
2.5.6.2	Synthesis of Phosphaalkenes	89
2.5.6.3	Synthesis of Silenes	90
2.5.6.4	Synthesis of Germenes	91
2.5.6.5	Synthesis of Sulfines	91
2.6	Conclusion	92
	References	93
3	The Julia Reaction	104
	<i>Raphaël Dumeunier and István E. Markó</i>	
3.1	Introduction	104
3.2	Historical Background	105
3.3	Coupling Between the Two Precursors of the Julia Reaction	106
3.3.1	Synthesis of Terminal Olefins	107
3.3.2	Preparation of 1,2-Disubstituted Olefins	109
3.3.3	Towards Trisubstituted Olefins	112
3.3.4	Towards Tetrasubstituted Olefins	114
3.3.5	Specific Considerations	115
3.3.5.1	Conjugated Olefins	115

3.3.5.2	Leaving Groups	115
3.3.5.3	Competitive Metallation on the Aromatic Ring of the Sulfone	118
3.4	Reductive Elimination	120
3.4.1	Sulfones Bearing Vicinal Hydroxyl Groups	122
3.4.2	Sulfones Bearing Vicinal Leaving Groups	127
3.4.3	Reverse Reductions	130
3.4.4	Reductions of Vicinal Oxygenated Sulfoxides	133
3.4.5	Reduction of Vinyl Sulfones	136
3.5	Second Generation Julia Reactions	136
3.6	Miscellaneous Julia Reactions	141
3.6.1	<i>gem</i> -Halogeno-Metal Electrophiles	141
3.6.2	Use of Sulfoximines	143
3.7	Conclusions	145
	References	146
4	Carbonyl Olefination Utilizing Metal Carbene Complexes	151
	<i>Takeshi Takeda and Akira Tsubouchi</i>	
4.1	Introduction	151
4.2	Carbonyl Olefination with Titanocene-Methylidene and Related Reagents	152
4.2.1	Preparation of Titanocene-Methylidene	152
4.2.1.1	The Tebbe Reagent	152
4.2.1.2	β -Substituted Titanacyclobutanes as Precursors of Titanocene-Methylidene	159
4.2.1.3	Zinc and Magnesium Analogues of the Tebbe Reagent	161
4.2.2	Higher Homologues of Titanocene-Methylidene	161
4.3	Carbonyl Olefination with Dialkyltitanocenes	166
4.3.1	Methylenation with Dimethyltitanocene	166
4.3.2	Alkylidenation of Carbonyl Compounds with Dialkyltitanocenes and Related Complexes	172
4.3.3	Allenation of Carbonyl Compounds with Alkenyltitanocene Derivatives	176
4.3.4	Carbonyl Olefination Utilizing an Alkyl Halide–Titanocene(II) System	176
4.4	Carbonyl Olefination Utilizing a Thioacetal-Titanocene(II) System	178
4.4.1	Formation of Titanocene-Alkylidenes from Thioacetals and Titanocene(II)	178
4.4.2	Alkylidenation of Aldehydes, Ketones, and Carboxylic Acid Derivatives	179
4.4.3	α -Heteroatom-Substituted Carbene Complexes	182
4.4.4	Intramolecular Carbonyl Olefination	182
4.4.5	Related Olefinations Utilizing <i>gem</i> -Dihalides	184
4.5	Carbonyl Olefination Using Zirconium, Tantalum, Niobium, Molybdenum, and Tungsten Carbene Complexes	185
4.5.1	Zirconium Carbene Complexes	185

4.5.2	Tantalum and Niobium Carbene Complexes	188
4.5.3	Molybdenum Carbene Complexes	189
4.5.4	Tungsten Carbene Complexes	192
4.6	Conclusion	194
	References	194
5	Olefination of Carbonyl Compounds by Zinc and Chromium Reagents	200
	<i>Seijiro Matsubara and Koichiro Oshima</i>	
5.1	Introduction	200
5.2	Zinc Reagents	201
5.2.1	Methylenation Reactions	202
5.2.1.1	By $\text{Zn}-\text{CH}_2\text{X}_2$	202
5.2.1.2	By $\text{Zn}-\text{CH}_2\text{X}_2-\text{TiCl}_n$	203
5.2.2	Alkylidenation Reactions	208
5.2.2.1	From <i>gem</i> -Dihaloalkanes	208
5.2.2.2	Via Carbometallation	211
5.2.3	Alkenylsilane, -germane, and -borane Synthesis	212
5.3	Chromium Compounds	214
5.3.1	Alkylidenation	214
5.3.2	Preparation of Alkenylboranes, -silanes, and -stannanes with <i>E</i> -Configuration	215
5.3.3	Preparation of (<i>E</i>)-Haloalkenes	215
5.4	Applications in Natural Product Synthesis	217
5.4.1	$\text{Zn}-\text{CH}_2\text{X}_2-\text{TiCl}_4$	218
5.4.2	$\text{CHX}_3-\text{CrCl}_2$	218
5.5	Conclusion	221
	References	221
6	The McMurry Coupling and Related Reactions	223
	<i>Michel Ephritikhine and Claude Villiers</i>	
6.1	Introduction	223
6.2	Scope of the McMurry Reaction	224
6.2.1	Intermolecular Coupling Reactions	224
6.2.1.1	Intermolecular Coupling of Aldehydes and Ketones	224
6.2.1.2	Intermolecular Coupling of Unsaturated Aldehydes and Ketones	226
6.2.1.3	Intermolecular Coupling of Aldehydes and Ketones with Functional Heteroatom Groups	228
6.2.1.4	Intermolecular Coupling of Organometallic Ketones and Aldehydes	235
6.2.1.5	The McMurry Reaction in Polymer Synthesis	237
6.2.1.6	Intermolecular Cross-Coupling Reactions	237
6.2.2	Intramolecular Coupling Reactions of Aldehydes and Ketones	240
6.2.2.1	Synthesis of Non-Natural Products	240
6.2.2.2	Synthesis of Natural Products	246
6.2.3	Tandem Coupling Reactions	249

6.2.4	Keto Ester Couplings	254
6.2.4.1	Intermolecular Keto Ester Couplings	254
6.2.4.2	Intramolecular Keto Ester Cyclizations; Synthesis of Cyclanones	255
6.2.4.3	Intramolecular Cyclizations of Acyloxycarbonyl Compounds; Synthesis of Furans	255
6.2.5	Intramolecular Couplings of Acylamidocarbonyl Compounds; Synthesis of Pyrroles and Indoles	256
6.2.6	Reductive Coupling of Benzyldene Acetals	258
6.3	Procedures and Reagents Used in the McMurry Reactions	259
6.3.1	Procedures	259
6.3.2	Reagents	260
6.3.2.1	The TiCl_4 - and TiCl_3 -Reducing Agent Systems	260
6.3.2.2	Effect of Additives on the TiCl_4 - and TiCl_3 -Reducing Agent Systems	261
6.3.2.3	Other Systems for the McMurry Alkene Synthesis: Organotitanium Complexes, Titanium Oxides, Titanium Metal	266
6.4	Mechanisms of the McMurry Reaction	266
6.4.1	Nature of the Active Species	267
6.4.2	Characterization of the Pinacolate Intermediates	268
6.4.3	Evidence of Carbenoid Intermediates	272
6.4.4	Mechanistic Analogies Between the McMurry, Wittig, and Clemmensen Reactions	273
6.4.5	The Different Pathways of the McMurry Reaction	274
6.5	Conclusion	275
	References	277
7	Asymmetric Carbonyl Olefination	286
	<i>Kiyoshi Tanaka, Takumi Furuta, and Kaoru Fuji</i>	
7.1	Introduction and Historical Aspects	286
7.2	Strategies for Asymmetric Carbonyl Olefination	289
7.3	Optically Active Phosphorus or Arsenic Reagents Used in Asymmetric Carbonyl Olefination	290
7.4	Discrimination of Enantiotopic or Diastereotopic Carbonyl Groups	299
7.4.1	Intermolecular Desymmetrization of Symmetrical Dicarbonyl Compounds	299
7.4.2	Intramolecular Discrimination Reactions	303
7.5	Discrimination of Enantiotopic or Diastereotopic Carbonyl π -Faces	306
7.5.1	Reactions with Prochiral Carbonyl Compounds	306
7.5.2	Reactions with Chiral Non-Racemic Carbonyl Compounds	311
7.5.3	Reactions with Prochiral Ketenes to give Dissymmetric Allenes	313
7.6	Kinetic Resolution	316
7.6.1	Resolution of Racemic Carbonyl Compounds	316
7.6.2	Resolution of Racemic Phosphorus Reagents	321
7.6.3	Parallel Kinetic Resolution	321
7.7	Dynamic Resolution	323

7.8	Further Application of Asymmetric Wittig-type Reactions in Enantioselective Synthesis	325
7.8.1	Use of Asymmetric Wittig-Type Reactions in the Total Synthesis of Natural Products	325
7.8.2	Sequential HWE and Pd-Catalyzed Allylic Substitutions	327
7.8.3	Tandem Michael–HWE Reaction	329
7.9	Asymmetric Carbonyl Olefinations Without Usage of Optically Active Phosphorus Reagents	329
7.10	Asymmetric Carbonyl Olefination by Non-Wittig-Type Routes	331
7.11	Concluding Remarks and Future Perspectives	336
	References	338
	Index	343

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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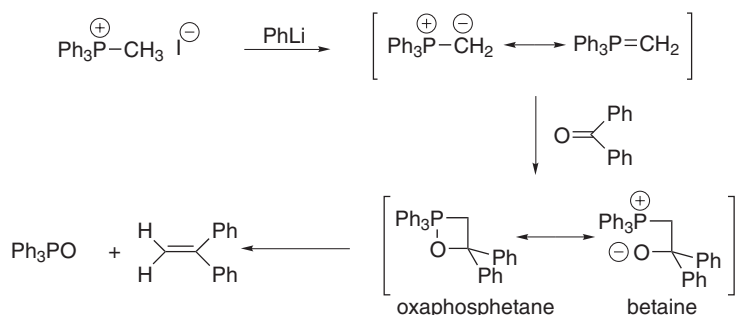
The Wittig Reaction

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]

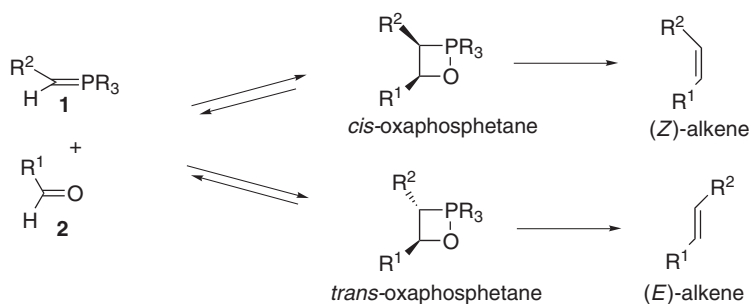
The original work of Wittig and Geissler [1], as depicted in Scheme 1.1, provides a good example of a classic Wittig reaction in which a phosphonium ylide reacts with an aldehyde or ketone to afford the corresponding alkene and phosphine oxide. This reaction is very general and provides a convenient 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

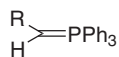
Nature of the Ylide and Carbonyl Compound

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.

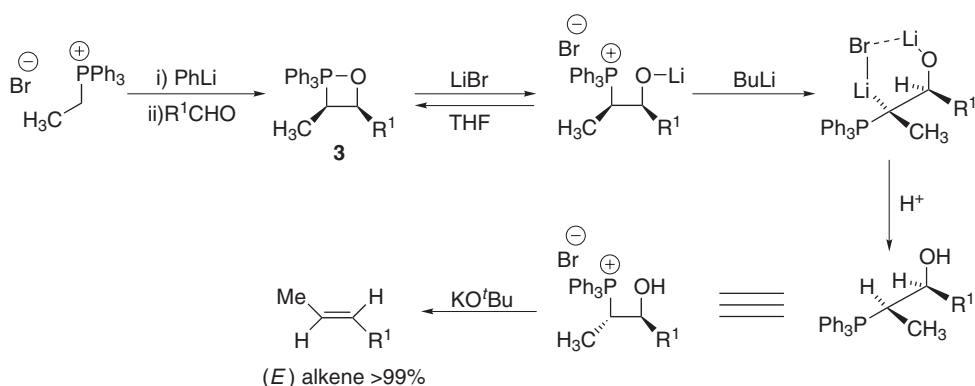
<i>Stabilized Ylides</i>	
<i>Factors that favor the E-alkene</i>	<i>Factors that disfavor the E-alkene</i>
Aprotic conditions	Li and Mg salts in DMF as solvent
A catalytic amount of benzoic acid ^[62]	Use of α -oxygenated aldehydes or methanol as solvent
<i>Non-stabilized Ylides</i>	
<i>Factors that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

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.

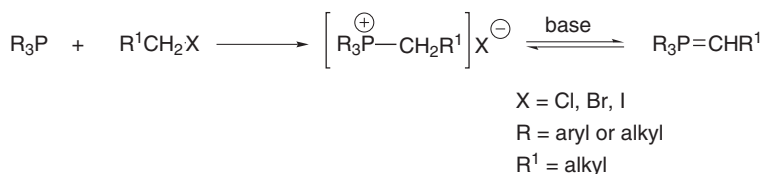
1.2.3

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].

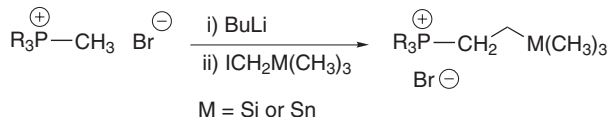
**Scheme 1.3.** The Schlosser modification.

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 allyl-silanes and -stannanes.

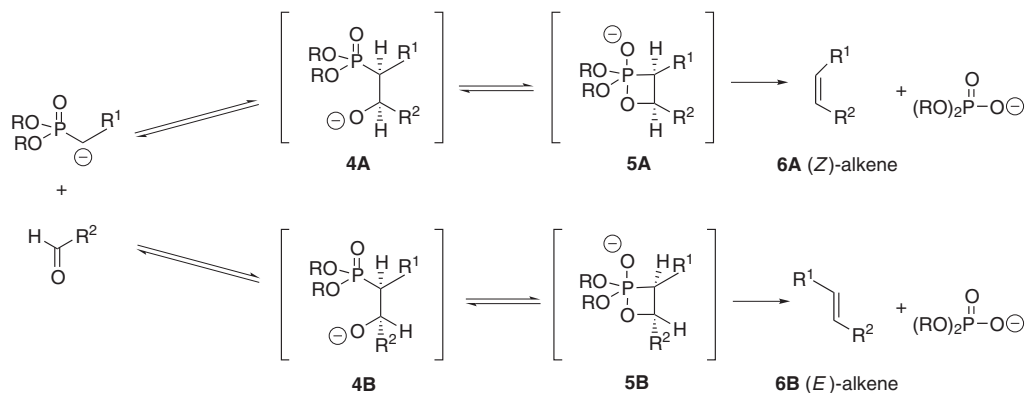


Scheme 1.5. Alkylation of phosphonium salts.

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 R² (for example COO^- , COOR , CN , SO_2R , vinyl, aryl $\text{P}(\text{O})(\text{OR})_2$, 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.

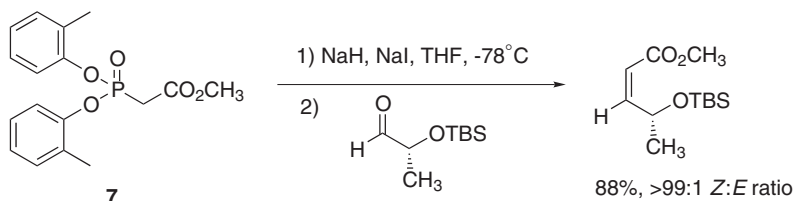
The so-called Ando method [21, 22] also provides access to a *Z*-alkene, as illustrated in Scheme 1.8 [23], where >99% *Z*-selectivity was obtained using



Reaction conditions

- | | |
|---|---------------------------------|
| a) (EtO) ₂ POCH ₂ CO ₂ Et, NaH, THF | 83%, <i>E</i> : <i>Z</i> = 12:1 |
| b) (CF ₃ CH ₂ O) ₂ POCH ₂ CO ₂ CH ₃ , KH, THF | 84% <i>E</i> : <i>Z</i> = 1:11 |

Scheme 1.7. The Still–Gennari modification.



Scheme 1.8. The Ando method.

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

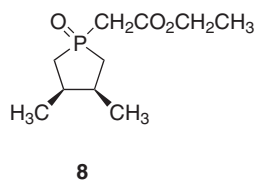
Some common factors that influence the stereochemical outcome of the HWE reaction are summarized in Table 1.2. In general, the addition of a phosphonate to a ketone occurs with moderate *E*-selectivity [24]. The reaction of an α -substituted phosphonate with an aldehyde also usually favors the *E*-alkene (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].

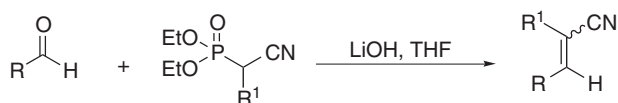
Substituents on the carbonyl compound can also influence the stereo-outcome of the HWE reaction. For example, carbonyl compounds that possess oxygenated groups at the α - or β -position generally favor the *E*-alkene [30, 31], although some exceptions have been observed [32].

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.

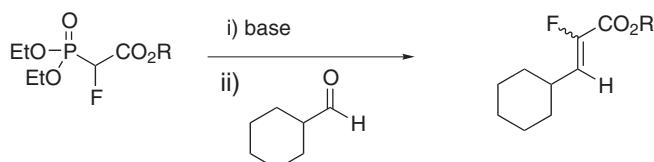
<i>Factors that favor the E-alkene</i>	<i>Factors that favor the Z-alkene</i>
Bulky R groups on the phosphonate e.g. $(\text{RO})_2\text{P}(\text{O})\text{--CH}(\text{--})\text{--R}$	Use of bis(2,2,2-trifluoroethyl) phosphonates (Still–Gennari modification)
Bulky R' groups adjacent to the carbanion e.g. $(\text{RO})_2\text{P}(\text{O})\text{--CH}(\text{--})\text{--R}'$	Use of cyclic phosphonates such as 8
Use of α -fluoro phosphonates	Use of (diarylphosphono)acetates (Ando method)/excess Na^+ ions





R	R ¹	E/Z, yield
Ph	H	90:10, 70%
Ph	CH ₃	77:23, 85%
nC ₇ H ₁₅	H	68:32, 74%
nC ₇ H 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.



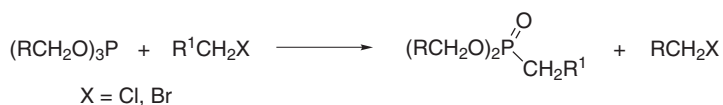
R	Base	E/Z, yield
Et	nBuLi	94:6, 83%
H	iPrMgBr	>1:99, 84%

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

1.3.2

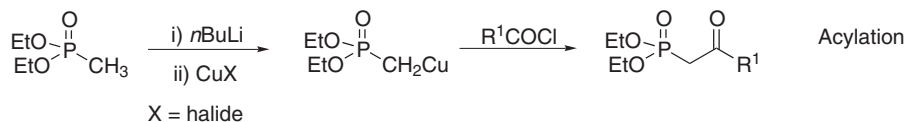
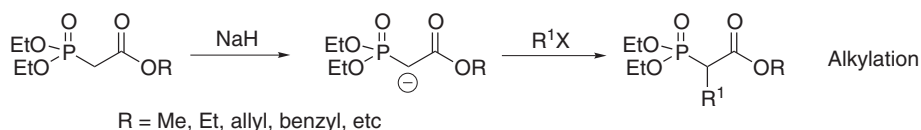
Reagents and Reaction Conditions

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).



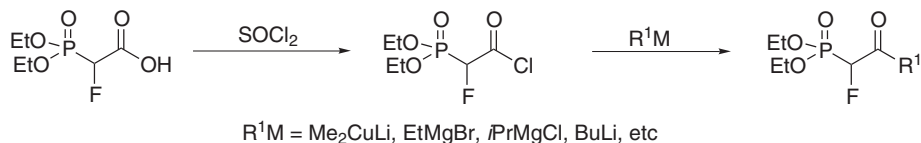
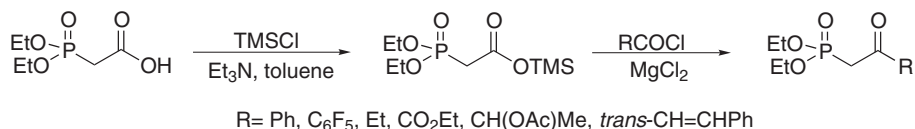
Scheme 1.11. The Michaelis–Arbuzov reaction.

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 di-alkyl phosphonoacetic acids [38] (Scheme 1.13).



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

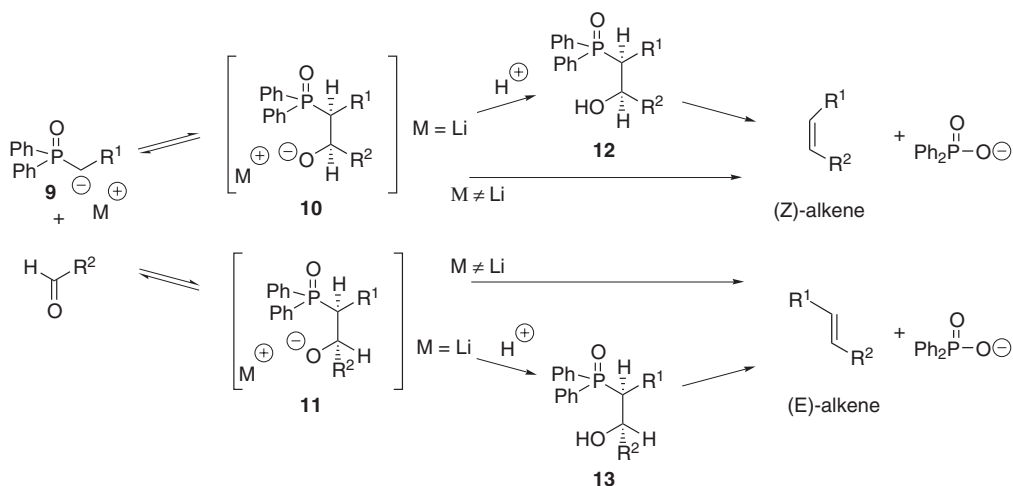
As stated above, phosphonates react with both aldehydes and ketones, although ketones generally require more vigorous conditions. Long chain aliphatic aldehydes tend to be unreactive, while readily enolizable ketones usually give poor yields of the alkene.

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 R¹ 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 R¹ 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-

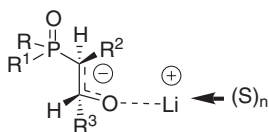


Fig. 1.2. Solvent-stabilized transition state model for the Horner–Wittig reaction.

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].

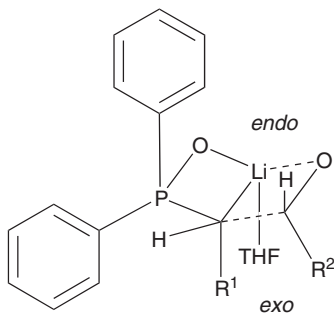
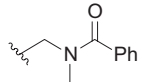
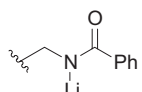
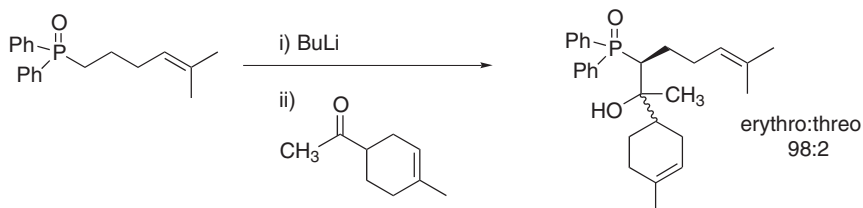


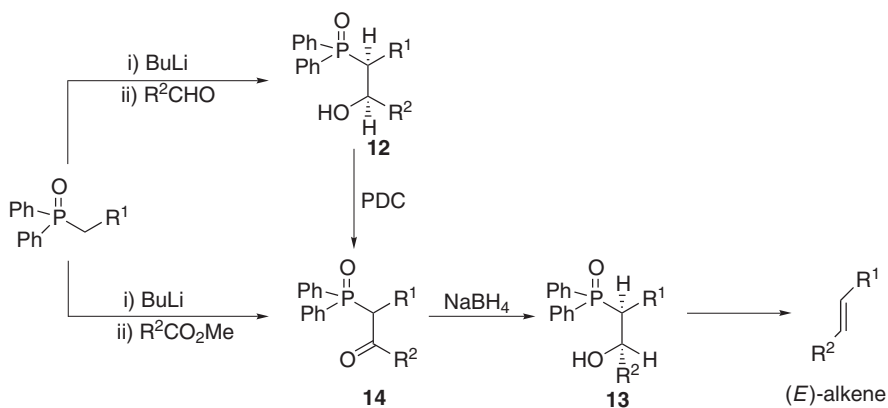
Fig. 1.3. Transition state model for the Horner–Wittig reaction.

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

R^1	R^2	Yield (%)	<i>Z/E</i> ratio
Me	Ph	88	88:12
Bu	Ph	84	84:16
<i>i</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>i</i> Pr	Pr	84	57:43
cyclohexyl	Pr	100	53:47
OMe	C ₆ H 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.