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Bridging McMurry and Wittig in One-Pot

Olefins from Stereoselective, Reductive Couplings of Two Aldehydes via Phosphaalkenes

JURI MAI

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Abstract

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The formation of C=C bonds is of great importance for fundamental and industrial synthetic organic chemistry. There are many different methodologies for the construction of C=C bonds in the literature, but currently only the McMurry reaction allows the reductive coupling of two carbonyl compounds to form alkenes. This thesis contributes to the field of carbonyl olefinations and presents the development of a new synthetic protocol for a one-pot reductive coupling of two aldehydes to alkenes based on organophosphorus chemistry. The coupling reagent, a phosphanylphosphonate, reacts with an aldehyde to yield a phosphaalkene intermediate which upon activation with a base undergoes an olefination with a second aldehyde.

A general overview of synthetic methods for carbonyl olefinations and the chemistry of phosphaalkenes is given in the background chapter. The Wittig reaction and its variations are discussed in detail. The synthesis, reactivity, properties and applications of phosphaalkenes are highlighted with particular focus on strategies to stabilize these otherwise reactive species.

The third chapter describes a novel method for the reductive coupling of aldehydes. The activation of phosphaalkene intermediates by a hydroxide base, mechanistic studies, development of a one-pot procedure and investigations of the substrate scope are discussed. The new one-pot reaction is advantageous over the McMurry coupling since it allows the formation of unsymmetrical *E*-alkenes under mild conditions.

The next chapter is dedicated to a modification of the reaction sequence. The results show that activation of the phosphaalkene with an alkoxide instead of hydroxide, followed by oxidation, generates a more reactive transient species that can undergo the coupling with electron rich (deactivated) aldehydes which was not possible under the initial reaction conditions.

Chapter five describes a modification of the phosphanylphosphonate reagent that enables the preparation of alkenes with high *Z*-stereoselectivity.

In the final chapter, chemical equilibria studies of triphenylphosphaalkenes are presented. It is found that phosphaalkenes with poor kinetic stabilization can also be used as intermediates in the carbonyl-to-alkene coupling chemistry.

In summary, this thesis presents the development of an unprecedented synthetic method for the direct formation of C=C double bonds from two aldehydes together with strategies on improvements of the substrate scope and modifications to control the stereochemical outcome of the reaction.

Keywords: carbonyl olefination, reductive aldehyde coupling, stereoselective, organophosphorus, phosphaalkene, phosphanylphosphonate, Wittig, Horner-Wittig, Horner-Wadsworth-Emmons, McMurry

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To my mother

”Chemical research and mountaineering have much in common. If the goal or the summit is to be reached, both initiative and determination as well as perseverance are required. But after the hard work it is a great joy to be at the goal or the peak with its splendid panorama.”[1]

GEORG WITTIG

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Esfandiarfard K., Mai J., Ott S. (2017) Unsymmetrical *E*-Alkenes from the Stereoselective Reductive Coupling of Two Aldehydes. *J. Am. Chem. Soc.*, 139(8): 2940–2943.

II Mai J., Arkhypchuk A. I., Gupta A. K., Ott S. (2018) Reductive coupling of two aldehydes to unsymmetrical *E*-alkenes *via* phosphaalkene and phosphinate intermediates. *Chem*. *Commun*., 54: 7163-7166.

III Mai J., Wagner S., Gupta A. K., Ott S. *Z*-selective alkene formation from reductive aldehyde homo-couplings. *Manuscript*

IV D'Imperio N., Arkhypchuk A. I., Mai J., Ott S. (2018) Triphenylphosphaalkenes in Chemical Equilibria. *Manuscript submitted to Eur. J. Inorg. Chem.*

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Contribution Report

Paper I	Performed half of the synthetic work and characterizations for the substrate scope. Contributed to the design of the project and the writing of the manuscript and the supporting information.
Paper II	Performed all of the synthetic work and characterizations, except for the X-ray crystallography. Wrote the manuscript and supporting information with feedback from S. Ott.
Paper III	Performed all of the synthetic work and characterizations, except for the X-ray crystallography. Major contributions to the interpretation of the results and the design of the project. Wrote the manuscript and supporting information with feedback from S. Ott.
Paper IV	Contributed to the synthetic work, the design and discussions of the project and writing of the manuscript.

Contents

1. Introduction 11

2. Background 13
  2.1 Formation of C=C bonds 13
    2.1.1 Carbonyl olefinations 14
    2.1.2 Olefinations with phosphorus – the WITTIG reaction 16
    2.1.3 Modifications of the WITTIG reaction 20
  2.2 Phosphorus as carbon analog 23
    2.2.1 P=C in comparison to C=C bonds 23
    2.2.2 Stabilization strategies for phosphaalkenes 24
    2.2.3 Synthetic routes towards phosphaalkenes 26
    2.2.4 Reactivity and applications of phosphaalkenes 28

3. Novel methodology for aldehyde-aldehyde couplings *via* phosphaalkene intermediates (Paper I) 32
  3.1 Alternative phosphorus-free aldehyde olefinations for 1,2-disubstituted *E*-alkenes 32
  3.2 Direct carbonyl-carbonyl couplings to olefins – the MCMURRY reaction 34
  3.3 Phosphaalkenes in the role of electrophiles 35
  3.4 Coupling reagent – preparation and application in the synthesis of phosphaalkenes 38
  3.5 Optimization of reaction conditions 39
    3.5.1 Mechanistic investigations by NMR studies 39
    3.5.2 Influence of the base 43
    3.5.3 Development of a one-pot procedure 44
  3.6 Substrate scope 46
    3.6.1 Symmetrical *E*-alkenes from homo-couplings 47
    3.6.2 Unsymmetrical *E*-alkenes from cross-couplings 48
  3.7 Mechanistic aspects on stereochemical outcome 51
  3.8 Advantages and limitations 53
  3.9 Conclusions 54

4. Method optimization and modification for broadening the substrate scope (Paper II) 56
  4.1 From HORNER-WITTIG to HORNER-WADSWORTH-EMMONS – strategies to overcome limitations 56

4.2 Substituent effects in phosphaalkenes 58
4.3 Reactivity enhancement *via* increased amount of oxygen substituents on intermediate phosphorus species 60
4.3.1 Nucleophilic addition of alkoxides to intermediate phosphaalkenes 61
4.3.2 Oxidation of intermediate phosphinites to phosphinates 63
4.3.3 Modified coupling sequence applied to one-pot protocol 64
4.4 Substrate scope 67
4.4.1 Unsymmetrical *E*-alkenes with push-pull electronic properties 67
4.5 Conclusions 69

5. Selective formation of *Z*-alkenes by a novel *phospha*-HWE coupling reagent (Paper III) 70
5.1 Stereoselective access to *Z*-alkenes – literature methods 70
5.2 Preparation of a new phosphanylphosphonate as *phospha*-HWE reagent 72
5.2.1 Synthetic approaches 72
5.2.2 Isolation and characterization 74
5.2.3 Unexpected side reaction and product 77
5.3 Reactivity towards aldehydes in a one-pot reaction 78
5.4 Substrate scope 81
5.4.1 Symmetrical *Z*-alkenes from homo-couplings 81
5.5 Mechanistic aspects on stereochemical outcome 83
5.6 Conclusions 85

6. Reducing steric bulk on phosphaalkenes – equilibria studies of triphenylphosphaalkenes (Paper IV) 86
6.1 Introduction 86
6.2 Synthesis of triphenylphosphaalkenes 87
6.3 Investigations on dimerization processes of triphenylphosphaalkenes 88
6.4 Conclusions 91

7. Outlook 92

8. Concluding remarks and summary 95

Svensk sammanfattning 98

Acknowledgments 102

References 104

Abbreviations

AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
Ar	Aryl or aromatic
Cp	Cyclopentadienyl ligand
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DFT	Density Functional Theory
DME	Dimethoxyethane
DMF	Dimethylformamide
Dmp	2,6-dimesitylphenyl
DMSO	Dimethyl sulfoxide
EDG	Electron donating group
Et	Ethyl
EtOH	Ethanol
EWG	Electron withdrawing group
Het	Heteroaryl or heterocyclic
HOMO	Highest occupied molecular orbital
HW	HORNER-WITTIG
HWE	HORNER-WADSWORTH-EMMONS
IP	Ionization potential
LDA	Lithium diisopropylamide
L_n	*n* number of ligands
LUMO	Lowest unoccupied molecular orbital
m-CPBA	*meta*-chloroperbenzoic acid
Me	Methyl
MeOH	Methanol
Mes	Mesityl (2,4,6-trimethylphenyl)
Mes*	Supermesityl (2,4,6-tri(*tert*-butyl)phenyl)
Mes^F	2,4,6-tris(trifluoromethyl)phenyl
NaHMDS	Sodium hexamethyldisilylamide
NMR	Nuclear Magnetic Resonance
OPA	Oxaphosphetane

PG	Protecting group
Ph	Phenyl
PPV	Poly(*p*-phenylene vinylene)
RDS	Rate determining step
SPO	Secondary phosphine oxide
TBAF	Tetrabutylammonium fluoride
TBAOEt	Tetrabutylammonium ethoxide
TBAOH	Tetrabutylammonium hydroxide
TBAOMe	Tetrabutylammonium methoxide
THF	Tetrahydrofuran
Tip	Triisopropylphenyl
TM	Transition metal
TMS	Trimethylsilyl
TS	Transition state

1. Introduction

Alkenes featuring carbon-carbon double bonds as the structural motif are ubiquitous in biologically active entities and serve as versatile starting materials for many different chemical transformations.[2] They are found in natural products such as lipids and vitamins and are important pharmaceutical products (*Figure 1.1*). For example, the anticancer drug Tamoxifen,[3] the stilbenoid and antioxidant Resveratrol,[4] and Rosuvastatin,[5] which was the fourth-highest selling drug in the United States in 2013,[6] have a characteristic C=C double bond in common. Alkenes are also key components in synthetic systems of many day-to-day objects such as plastics, dyes, and pigments. They are used as model compounds for studies in physical organic chemistry and in the field of organic electronics.[7] In this context, the stereochemistry of the alkenes is a central aspect since it determines the property of the molecules and in the case of drugs can influence the pharmacological activity. The stereodefined synthesis of either the *E*- or the *Z*-isomer is crucial and has been one of the major topics in synthetic organic chemistry for many decades.[2j, 8] Along these lines, the discovery of novel methodologies for a stereoselective formation of C=C double bond containing compounds from feedstock starting materials is at the heart of organic chemistry.

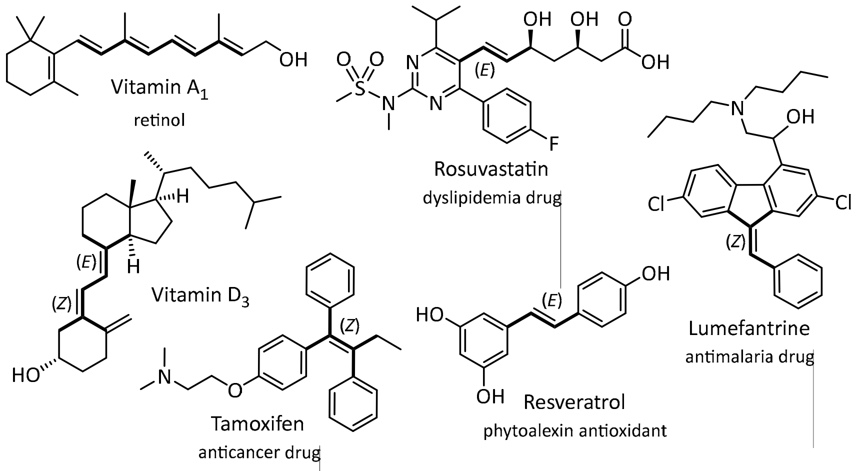

Vitamin A_1
retinol
OH
Rosuvastatin
dyslipidemia drug
(E)
OH OH O
OH
N
N
N
S
O O
F
Lumefantrine
antimalaria drug
N
OH
Cl
Cl
(Z)
Vitamin D_3
H
H
(E)
(Z)
HO
Tamoxifen
anticancer drug
N
O
(Z)
Resveratrol
phytoalexin antioxidant
HO
OH
OH
(E)

Figure 1.1 Selected examples of vitamins and drug molecules with a C=C double bond motif.

When developing new synthetic protocols, the control of selectivity and yields remain at the center of optimization efforts. This thesis is devoted to the development of a new methodology for a *direct* and stereoselective formation of C=C double bonds from readily available aldehydes. The new concept uses phosphaalkenes as key intermediate species.

Particular attention is paid to modifications which enable a broader substrate scope and the control of the stereochemical outcome. With this, the aim of the work presented in here is to broaden the toolbox of preparative methods for olefinic compounds.

2. Background

This chapter provides a general perspective on different methods for the formation of carbon-carbon double bonds and the chemistry of phosphaalkenes. Carbonyl olefination methodologies that utilize organophosphorus reagents and corresponding modifications are presented with the aim to make the reader familiar with common synthetic approaches towards alkenes. This enables a better understanding of the contribution of this thesis to the field of carbonyl olefinations.

2.1 Formation of C=C bonds

As already pointed out in the introduction, the formation of carbon-carbon double bonds is of paramount importance and has an immense impact on fundamental and industrial synthetic organic chemistry.[2a, 2b, 2f, 2j, 9] This is mainly due to the ubiquitous presence of alkenes in a wide range of natural as well as synthetic molecules. Moreover, the C=C double bond is a versatile functionality for numerous chemical transformations. An illustrative listing of various reactions for the formation of carbon-carbon double bonds is shown in *Figure 2.1*.

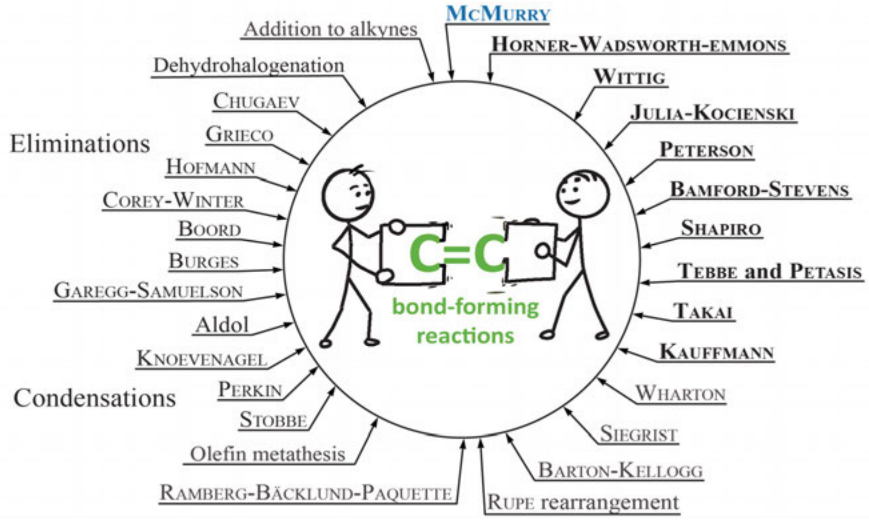
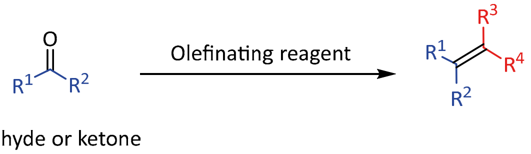

Addition to alkynes
McMurry
Horner-Wadsworth-emmons
Dehydrohalogenation
Wittig
Chugaev
Julia-Kocienski
Eliminations
Grieco
Peterson
Hofmann
Bamford-Stevens
Corey-Winter
Shapiro
Boord
Burges
Tebbe and Petasis
Garegg-Samuelson
Takai
Aldol
Kauffmann
Knoevenagel
Wharton
Condensations
Perkin
Stobbe
Siegrist
Olefin metathesis
Barton-Kellogg
Ramberg-Bäcklund-Paquette
Rupe rearrangement
C=C
bond-forming
reactions

Figure 2.1 List of various Name Reactions for C=C bond formation.[10]

Many carbon-carbon double bond forming reactions are either eliminations or condensations which often use aldehydes or ketones as starting materials. There are a handful of methods that use a specific reagent to transform a carbonyl functionality into the corresponding alkene, namely the Wittig, Horner-Wadsworth-Emmons, Julia-Kocienski, Takai, Tebbe, Petasis, Peterson, Shapiro, Bamford-Stevens, and Kauffmann reactions (**bold** in *Figure 2.1*). These reactions provide a range of chemo- and stereoselectivities and are utilized in a broad variety of organic syntheses. But among all the different approaches towards carbon-carbon double bonds there is only one method that uses *directly* two carbonyl groups to form an olefin, namely the McMurry coupling (**blue** in *Figure 2.1*).[11]

2.1.1 Carbonyl olefinations

Olefination methods that utilize a specific reagent, which reacts with a carbonyl group to form an olefin, are some of the most fundamental conversions in organic synthesis.[2f, 9] A general scheme of such a transformation is depicted in *Scheme 2.1*. Hence, a variety of synthetic protocols, that are all "*classical*" Name Reactions,[10a] have been developed. In particular, methods that focus on the chemical properties of main group elements such as phosphorus, silicon, and sulphur have been intensively studied.



Scheme 2.1 General reaction scheme for the olefination of an aldehyde or ketone using a specific reagent.

One of the most representative carbonyl olefination is the Wittig[1, 12] reaction and its Horner-Wittig[13] (HW) and Horner-Wadsworth-Emmons[14] (HWE) variations which will be described more detailed in the following sections. Other similar reactions are the silicon-mediated Peterson[15] olefination and the sulphur-based Julia-Lythgoe[16] and Julia-Kocienski[17] reactions. Both are very useful methods and widely applied in the synthesis of carbon-carbon double bond containing molecules. The corresponding olefinating reagents for each of these reactions are shown in *Figure 2.2*.

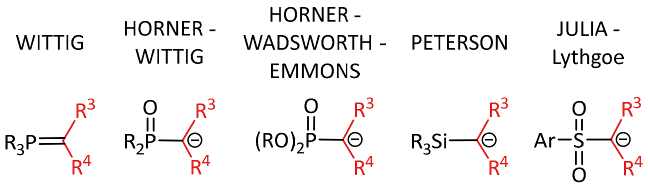
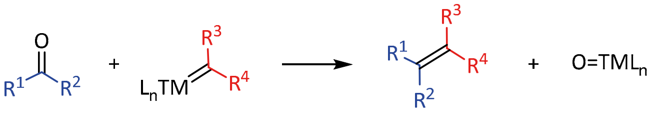

WITTIG
HORNER - WITTIG
HORNER - WADSWORTH - EMMONS
PETERSON
JULIA - Lythgoe
R3P
R2P
(RO)2P
R3Si
Ar–S
O
R3
R4

Figure 2.2 Organo main group reagents for the olefination of carbonyl compounds. The corresponding NAME REACTIONS are written above.

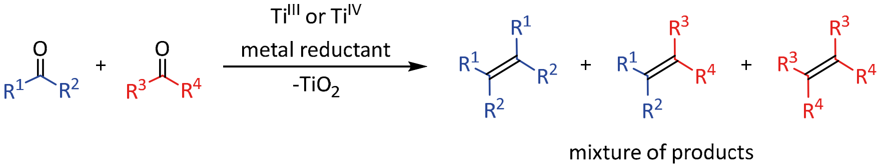
In addition to main group elements, some transition metals can also drive the olefination of a carbonyl functionality. In particular, transition metal-carbene complexes with the general structure $L_nTM{=}CR^3R^4$ have become an indispensable tool in the synthesis of various olefins.[18] The Schrock-type carbene complexes with high-valent early transition metals without π-accepting ligands are nucleophilic in nature, and show ylide-like reactivity towards carbonyl compounds (*Scheme 2.2*).[19]


O
R1
R2
+
LnTM
R3
R4
O=TMLn

Scheme 2.2 Carbonyl olefination utilizing transition metal-carbene complexes as olefinating reagents.

Among numerous early transition metals, titanium has proved to have a unique ability to couple a wide range of aldehydes and ketones to olefins.[20] Organotitanium species, like the Tebbe[21] or Petasis[22] reagents, are very useful not only for the methylenation of aldehydes and ketones, but also for esters, lactones, amides and thioesters. In both cases the active complex is a titanocene methylidene $Cp_2Ti{=}CH_2$.[23]

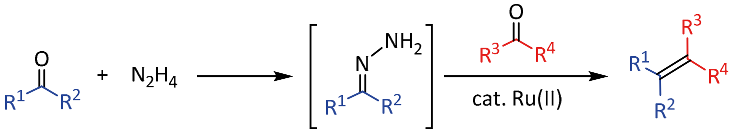
A *direct* coupling of two carbonyl groups, which is the McMurry reaction, can be achieved with low-valent titanium species.[20a, 24] In here, a titanium(III) or (IV) precursor in combination with a reductant couples two carbonyl functionalities to form an alkene (*Scheme 2.3*). In this reaction, *in situ* produced low-valent titanium functions as electron donor and oxygen acceptor.


O
R1
R2
R3
R4
Ti^III or Ti^IV
metal reductant
-TiO2
mixture of products

Scheme 2.3 McMurry coupling of two different carbonyl groups leading to a mixture of symmetrical and unsymmetrical products.

The McMurry coupling works well for symmetrical alkenes but usually yields product mixtures if two different carbonyl groups are coupled.[11]

Noteworthy is a recently reported carbonyl-carbonyl coupling method that is mediated by hydrazine in the presence of a ruthenium(II) catalyst.[25] This method enables the selective coupling of two different carbonyl compounds and proceeds under mild reaction conditions with good functional group tolerance (*Scheme 2.4*).

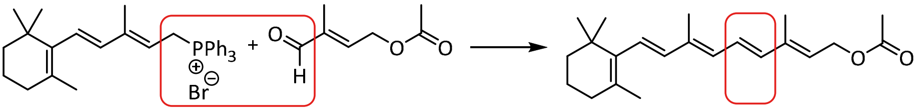


Scheme 2.4 Ruthenium(II) catalysed carbonyl cross-coupling with a hydrazone intermediate. This method was first reported by the group of Li *et al* in 2017.[25]

More detailed and mechanistic descriptions of the mentioned methods which utilize low-valent titanium or non-phosphorus main group elements are presented in sections 3.1 and 3.2.

2.1.2 Olefinations with phosphorus – the Wittig reaction

Since its discovery in 1953 by Wittig and Geissler,[12a] the olefination of carbonyls with phosphonium ylides has gained tremendous importance in the preparation of various types of alkenes.[1, 2b, 2j, 10b, 26] Nowadays, the Wittig reaction is perhaps the most commonly used method for the synthesis of alkenes.[10a, 26c] It is also applied on an industrial scale, for instance as the key step for the synthesis of Vitamin A (*Scheme 2.5*).[27] Over 1000 tons are produced annually by BASF and in 2016 BASF announced the building of a new factory for the Vitamin A synthesis which will increase the output by 1500 tons per year.[28]



Scheme 2.5 Synthesis of Vitamin A acetate by a Wittig reaction between a C_{15} phosphonium ylide and a C_5 aldehyde.[27]

The phosphonium ylide can be represented by two resonance structures shown in *Figure 2.3* either in the fully ionic ylide form or in the ylene form. It is important to mention at this point that the P-C bond is heavily polarized towards carbon.[29] Depending on the substituent R^3 attached to the α-carbon the distinction between non-stabilized, semi-stabilized, and stabilized ylides has to be made. Here, stabilization accounts for the negative charge at the α-carbon atom.[26b]

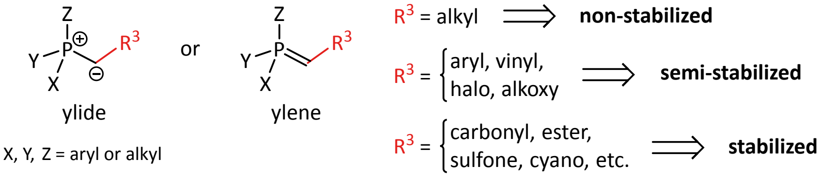
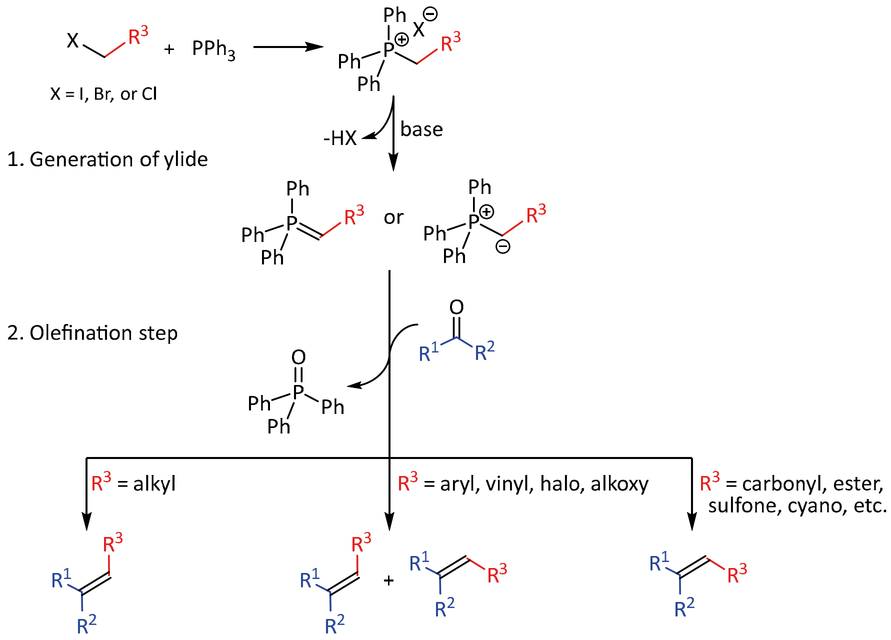


Figure 2.3 General classification of ylides. R^3 may be alkyl, aryl, vinyl, or an electron-withdrawing group (e.g. carbonyl, ester, *etc*.).

The WITTIG reaction is utilized in the synthesis of many complex molecules as the ylides are tolerant to a number of different functional groups (e.g. hydroxyl, amino, halo, amide, cyano, ester, aromatic nitro).[30] Most frequently, triphenylphosphonium ylides ($Ph_3P=CHR^3$) are employed since they are readily formed by the reaction of inexpensive and air-stable triphenylphosphine with alkyl halides followed by addition of suitable bases to the phosphonium salt (see upper part in *Scheme 2.6*). The reactivity of the ylides is dependent on the R^3 substituent. For non-stabilized (e.g. R^3 = alkyl) and semi-stabilized (e.g. R^3 = aryl, vinyl, halo, alkoxy) ylides the reactivity is high, and they react essentially instantaneously or in a matter of seconds or minutes at low temperatures.[26c] Since they are unstable towards moisture and oxygen, *in situ* preparation is usually carried out at -78 °C under inert conditions. Strong bases such as LDA, *n*-BuLi, $NaNH_2$, NaHMDS, or *t*-BuOK are used to generate the ylide. In contrast, stabilized ylides with a strong electron-withdrawing group (R^3 = carbonyl, ester, sulfone, cyano, *etc*.) are less reactive and usually isolable. They are prepared using weaker bases such as aqueous NaOH.[30]

In general, the carbonyl reactant may be formaldehyde, aldehydes or ketones which enables the synthesis of mono-, di-, and trisubstituted alkenes. In some cases, additives (e.g. lithium salts,[31] phase transfer catalysts,[32] or silica gel[33]), high pressure,[34] microwave irradiation,[35] ionic liquids[36] or solvent-free conditions[37] have been utilized in order to improve yields or stereoselectivity.

The stereochemistry is primarily determined by the nature of the phosphonium ylide, although some other variables such as base, type of counter ion, solvent and temperature may have an effect as well.[10a] Essentially, non-stabilized ylides under Li salt-free conditions yield preferentially *Z*-alkenes, whereas *E*-alkenes are obtained for stabilized ylides, and a product mixture of *Z*- and *E*-isomers is formed for semi-stabilized ylides. The corresponding reaction pathway is represented in *Scheme 2.6*.[10a, 26c, 30]

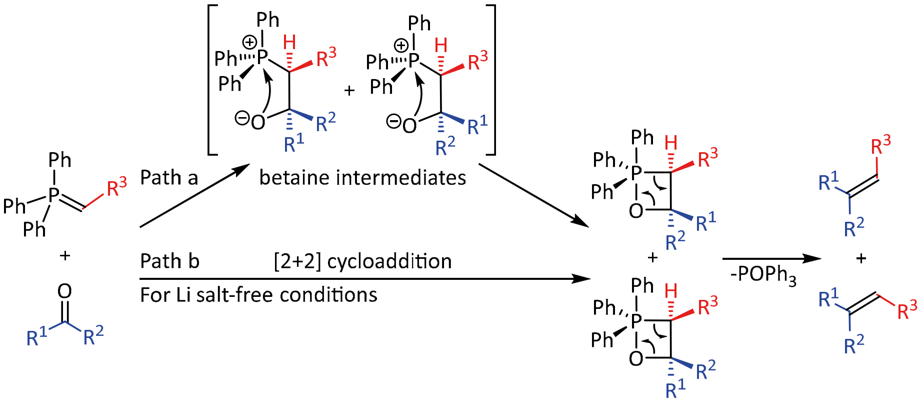


Scheme 2.6 Preparation of phosphonium ylides and general stereochemical outcome depending on the substituent of the ylide. The carbonyl reactant can be an aldehyde ($R^1 = R^2 = H$, or R^1 = alkyl/aryl, $R^2 = H$) or a ketone (R^1 = alkyl/aryl, R^2 = alkyl/aryl).[26c, 30]

The stereoselectivity can be tuned further. One strategy is the modification of the P-phenyl groups of triphenylphosphonium ylides. For example, *ortho*-substitution of the aryl groups on the ylide P-atom is effective in enhancing *Z*-selectivity for reactions with semi-stabilized ylides.[38] Another important way for tuning the stereochemical outcome is the SCHLOSSER modification.[10a, 39] It allows a selective formation of *E*-alkenes from non-stabilized ylides when two equivalents of Li-halide salt (e.g. LiBr) are present in the reaction mixture.[40]

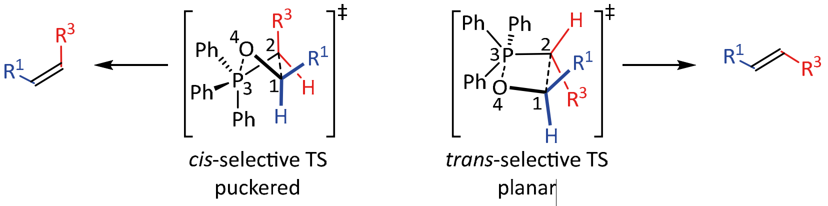
The mechanism of the WITTIG reaction was originally thought to occur in three steps:[12b, 41] nucleophilic addition of the ylide to the aldehyde or ketone to yield a betaine; rotation along the C-C bond of the betaine to form an oxaphosphetane (OPA); decomposition to the alkene product and phosphine oxide by-product (Path a in *Scheme 2.7*).[26c, 30] The presence of OPA as intermediates is doubtless because they have been detected by low-temperature ^{31}P, ^{1}H, and ^{13}C NMR spectroscopic analysis in reactions of non-stabilized and semi-stabilized phosphonium ylides.[42] Contrary, there is no spectroscopic evidence for betaines under Li salt-free reaction conditions.[26c, 43] These species have only been observed in the presence of strongly coordinating ions such as lithium.[42b, 44]

In the modern interpretation of the mechanism, all reactions under Li salt-free conditions proceed *via* an oxaphosphetane as the only intermediate (Path b in *Scheme 2.7*) which is formed directly by an irreversible [2+2] cycloaddition of the ylide with the carbonyl through a four-center transition state (TS) and under kinetic control.[26c, 30, 42a, 45]



Scheme 2.7 Mechanism of the WITTIG reaction.[26c, 30]

The stereochemical outcome of the reaction is decided during the formation of the OPA and is a result of steric effects when the ylide and aldehyde approach each other.[30, 46] Among all the proposed transition state models, the one by VEDEJS accounts best for the stereoselectivity. It is based on an interplay of 1,2- and 1,3-steric interactions (*Scheme 2.8*).[45, 47]



Scheme 2.8 Transition state structures for the irreversible [2+2] cycloaddition according to VEDEJS model (with R^2 = H).[30, 45b, 47a]

In case of non-stabilized ylides, the addition to aldehydes (or ketones) proceeds through an early and flexible TS with a preferred *cis* geometry where the P-atom is in a nearly tetrahedral geometry. In order to relieve steric interactions between the ylide substituents and the aldehyde (1,2-interactions) and between the aldehyde substituents and the P-substituents (1,3-interactions) the TS is puckered. Thus, the formation of *cis*-OPA is under kinetic control and followed by irreversible and stereospecific decomposition to *Z*-alkenes and phosphine oxides *via syn*-cycloreversion.[26c, 45b, 48] Stabilized ylides react through a later, less flexible, and more planar TS where bond formation and rehybridisation are more advanced with a trigonal bipyramidal geometry of the substituents around phosphorus. Since a *cis*-orientation in such a planar

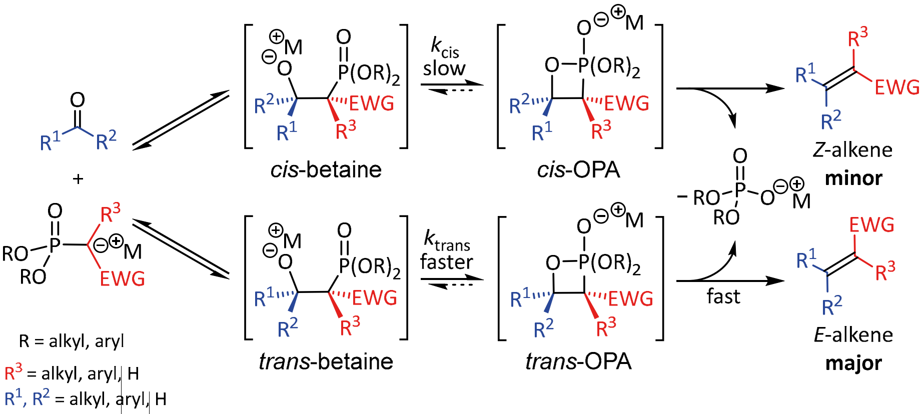
TS would seriously suffer from torsional strain between R^1 and R^3 (1,2-interactions), a *trans* TS is favored and the reaction yields *E*-alkenes (compare in *Scheme 2.8*).

To conclude the mechanistic discussion, it should be clearly stated that the Li salt-free mechanism is known whereas the Li-present one is still effectively unknown.[26c]

2.1.3 Modifications of the WITTIG reaction

A very important and widely applied modification of the WITTIG olefination is the HORNER-WADSWORTH-EMMONS (HWE) reaction.[10a, 14, 26b] In 1958, HORNER disclosed a WITTIG-type reactivity for phosphonate stabilized carbanions,[13a, 49] the scope of which was further defined by WADSWORTH and EMMONS.[14a, 50] The carbanions are typically stabilized by electron-withdrawing groups (i.e. the α-C-atom has an R^3 substituent and an additional EWG) such as ester, sulfonyl, or cyano groups, and are more nucleophilic and basic than their phosphonium ylide congeners.[50] The reaction works for both aldehydes and ketones, although harsher conditions are required for ketones. Hindered ketones which are unreactive in WITTIG reactions engage in HWE chemistry.[10a, 26b] A big advantage of the HWE reaction is that the phosphate by-products are water soluble and thus easier to separate from the alkene products by simple aqueous extraction. The starting phosphonates are usually prepared by means of the MICHAELIS-ARBUZOV reaction of trialkyl phosphites with corresponding organic halides.[51] The stereochemical outcome is in some way dependent on the nature of the phosphonate. Usually, in case of aldehydes the formation of *E*-alkenes is favored.[10a] A higher *E*-selectivity is achieved for bulky substituents R^3, bulky EWGs, and elevated reaction temperatures.[52]

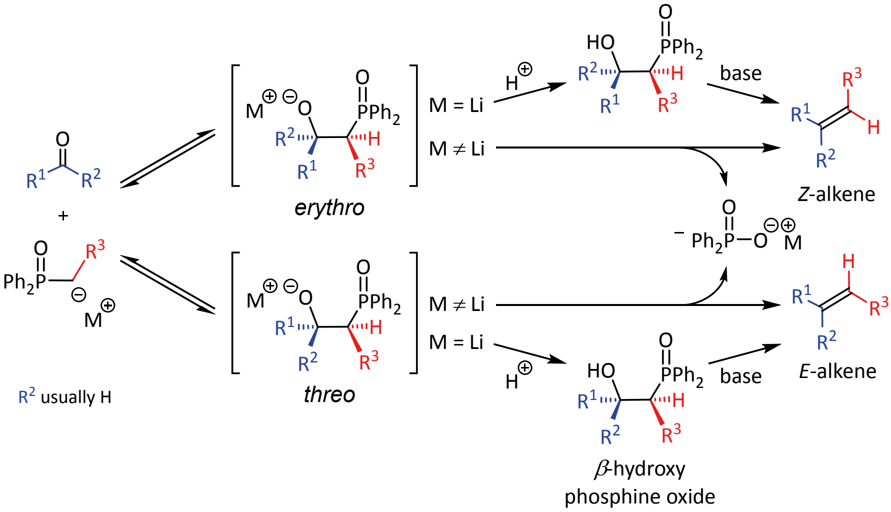
The commonly accepted mechanism is depicted in *Scheme 2.9*.[14b, 26b] The reaction proceeds through a betaine intermediate that is in equilibrium with the corresponding oxaphosphetane. The final step, the decomposition of the OPA to the alkene product and the phosphate, is irreversible. Thus, the stereoselectivity of the reaction depends upon the initial reversible addition to the carbonyl and the ability of the intermediates to equilibrate.[26a] Due to a faster elimination to the *E*-alkene than to the Z-isomer, the reaction gives in general *E*-alkenes as the major product. Additionally, the ratio for the *E*-isomer can be further increased by conditions that raise the rate for the retro-addition.[52] According to computational studies the highest barrier is for the formation of the OPA which is of marginal stability and proceeds rapidly to the product.[53]



Scheme 2.9 Mechanism of the HWE reaction.[10a, 26b]

The main disadvantage of the reaction is that EWGs are necessary for the stabilization of the α-carbanion and the final elimination step to occur. In case of non-stabilized phosphonates (R^3 = alkyl or aryl without additional EWG) the reaction is slow and often stops at the betaine step yielding *β*-hydroxyphosphonates after work-up.[26b, 50, 54]

Another modification is the HORNER-WITTIG (HW) reaction that uses phosphine oxides instead of phosphorus ylides.[26b, 55] In 1959, HORNER and coworkers showed that the treatment of diphenylphosphine oxides with a base and a subsequent addition of an aldehyde or ketone gives alkenes.[13] An advantage of the HW-reaction is the possibility to control the stereochemical outcome by choosing different bases. When bases such as *t*-BuOK are used, the alkenes are formed directly in one step, while the use of lithium bases allows the intermediate *β*-hydroxy phosphine oxide diastereomers to be isolated and separated.[13a] In the second step, each diastereomer can be treated separately and, after addition of another base, the corresponding alkenes are formed *via* an OPA with high stereochemical purity (see *Scheme 2.10* for an overall mechanism). A phosphinate by-product is formed which is water-soluble and hence, readily removed from the desired olefinic product similarly to the HWE reaction.



Scheme 2.10 General scheme for the HORNER-WITTIG reaction.[26b]

In a “one-step” HW-olefination with non-lithium bases or anion stabilizing R^3 groups HW elimination follows directly after HW addition without isolation of the β-hydroxy phosphine oxides.[55] Under these conditions the formation of the *erythro* and *threo* intermediates is reversible. Usually *E*-alkenes are formed preferentially since the *syn*-elimination from the *threo* intermediate occurs much faster than from the corresponding *erythro* intermediate.[26b]

However, for unstabilized lithiated phosphine oxides neither the reverse reaction nor the elimination takes place. Aqueous quenching does not give an alkene but often a stable, crystalline β-hydroxy phosphine oxide.[56] The use of a lithium base is crucial for this since the lithium counterion binds strongly to the oxyanion from the aldehyde or ketone and thus prevents it from attacking the electrophilic Ph_2PO group. Under these conditions the *erythro* intermediate predominates and after the elimination step an alkene with high *Z*-selectivity is formed. But in most cases a diastereomeric mixture is formed which then can be separated by column chromatography or crystallization.[56] Treatment of each pure diastereomer with a sodium or potassium base (e.g. NaH in DMF or KOH in DMSO) generates a more nucleophilic oxyanion which after attack on the Ph_2PO group and *syn* elimination leads to the corresponding single stereoisomer.[57] Such a stepwise sequence (HW addition, purification of the intermediate, HW elimination) is called stereocontrolled HW reaction.[56]

2.2 Phosphorus as carbon analog

At first glance on phosphorus and carbon, which are located in group 15 and 14 of the periodic table, one might expect quite different structural properties, bonding behavior, and reactivity for the two elements. However, in low coordination numbers of one and two it has been shown that phosphorus bears a close resemblance to carbon.[58] This is often referred to as "carbon copy"[59] or "carbon photocopy"[60] in the literature.

The P-C analogy was drawn due to the ability of phosphorus to accept and release electrons similarly to carbon. For example, the first ionization potential (IP) of phosphorus is relatively close to that of carbon (IP_P = 1011.8 kJ/mol, and IP_C = 1086.5 kJ/mol).[61] Both elements have also very similar valence orbital ionization energies which are -18.8 eV (3s) and -10.1 eV (3p) for phosphorus and -19.4 eV (3s) and -10.6 eV (3p) for carbon.[62] Most importantly is the comparison of the electronegativities. While the σ electronegativity of phosphorus is slightly lower than that of carbon (2.1 *vs*. 2.5, respectively according to Pauling scale), the effective π electronegativities are nearly the same.[63]

2.2.1 P=C in comparison to C=C bonds

Phosphaalkenes contain a P=C double bond where the phosphorus atom has a valency of three (λ^3) and a coordination number of two (σ^2).[58a] The P=C bond resembles the C=C bond in many aspects owing to the related characteristics of phosphorus and carbon atoms linked by their diagonal relationship and that phosphorus is isolectronic with the C-H fragment.[64] Due to these similarities, phosphaalkenes can also be referred to as a "heavy olefin".

As a result of minor difference in the values for the π component of the electronegativity the (3p-2p)π-bond in phosphaethene ($H_2C{=}PH$) is comparable to that of the (2p-2p)π-bond of ethene ($H_2C{=}CH_2$), whereas the σ component is highly polarized ($P^{\delta+}$-$C^{\delta-}$).[65] For a better understanding of the chemical reactivity of compounds containing a P=C unit, it is interesting to compare the highest occupied molecular orbital (HOMO) of $H_2C{=}PH$ with its carbon analog $H_2C{=}CH_2$ (*Figure 2.4*).

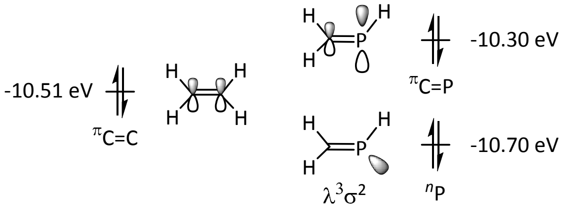


Figure 2.4 Comparison of HOMO energy levels between $H_2C{=}CH_2$ and $H_2C{=}PH$.[66]

Both HOMO levels are very close in energy to each other. As indicated in *Figure 2.4*, the π ionization energy of ethene is only 0.21 eV lower than that of phosphaethene.[66] This means that in general, the π-system in phosphaalkenes is expected to show a higher reactivity than the one in alkenes.[67] Since the P lone pair (n_P) is only 0.40 eV lower in energy than the π-bond, it tends also to contribute to the overall reactivity.[59] Additionally, this high reactivity is confirmed by some thermodynamic data which show that the P=C π-bond is significantly weaker than its carbon congener (calculated π-bond energies: for $HP{=}CH_2$ 45 kcal/mol, and for $H_2C{=}CH_2$ 65 kcal/mol).[68]

Despite the similarities described above, there are few important differences to mention at this point. These are in particular the availability of the lone pair as an alternative binding site for complexation with transition metals,[64a] and the possibility of oxidative addition at the P^{III} center.[58a] Moreover, the considerably lower energy level of the LUMO in phosphaalkenes which results in a smaller and variable HOMO-LUMO band gap in compounds containing a P=C unit.[64b, 67, 69] In fact, this is the origin for some very interesting photophysical properties of phosphaalkenes which gave rise to many recent applications in the field of polymer science, organic electronics and optoelectronics (more detailed in section 2.2.4).[60, 64b, 70]

2.2.2 Stabilization strategies for phosphaalkenes

As described above, phosphaalkenes are highly reactive and not stable under ordinary conditions unless some stabilization is provided in the form of conjugation or delocalization (thermodynamic), complexation or steric hindrance (kinetic).[58b, 67]

Thermodynamic stabilization of the P=C unit can be achieved in delocalized and cyclic systems like in the prominent examples of 2,4,6-triphenylphosphabenzene and parent phosphabenzene synthesized by MÄRKL[71] and ASHE,[72] respectively.

In terms of metal complexations, phosphaalkenes are able to form stable complexes with transition metals (TM) in different coordination modes where the P-atom acts as σ-electron donor *via* the lone pair and as π-electron acceptor due to the low energy of the π*-system (*Figure 2.5*).[59, 64a, 73]

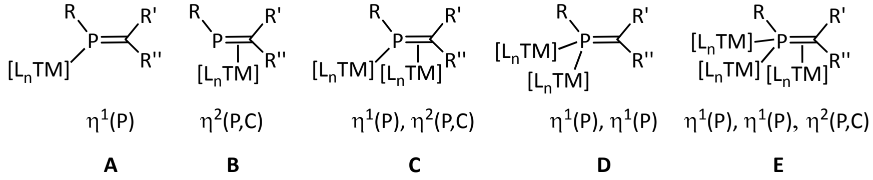


Figure 2.5 Various modes of phosphaalkene coordination to transition metals.[73c]

Complexation through the P lone pair (type A, η^1(P) in *Figure 2.5*) is the most common coordination motif. When coordinated, the P=C bond is unaffected and still available for reactions.[64a, 74] In complexes of type B the metal coordinates to the π-system of the P=C bond, and ligand-to-metal electron donation from the π-orbital (HOMO) and metal-to-ligand backdonation into the π*-orbital (LUMO) result in P=C bond elongation. In some cases an increased coordination number from three to four at the P-atom is observed (see type D and E in *Figure 2.5*).[75] Due to this rich coordination chemistry, numerous phosphaalkenes have found diverse applications as ligands in catalytic reactions such as hydrogenations, hydroaminations, and cross-couplings (more details in section 2.2.4).[76]

Relevant to this thesis is the protection of localized phosphaalkenes in acyclic compounds by means of kinetic stabilization.[64a] Usually, this is achieved by blocking either the P- or C-atom with sterically demanding groups. If the group is extremely bulky, the corresponding phosphaalkene is protected from hydrolysis and oligomerization, and isolation through classical chromatographic purification becomes possible. This strategy is well known and commonly used in phospha-organic chemistry.[77] Many examples of protecting groups (PG) were reported during the past decades, the most commonly used being 2,4,6-tri(*tert*-butyl)phenyl (Mes* or supermesityl), 2,4,6-triisopropylphenyl (Tip), 2,4,6-trimethylphenyl (Mes or mesityl), 2,6-dimesitylphenyl (Dmp), *tert*-butyl, tris(trimethylsilyl)methyl, trimethylsilyl (TMS), and adamantyl.[77b] Their molecular structures are represented in *Figure 2.6*. In general, the stability of phosphaalkenes decreases with decreasing bulkiness of the protecting group in the order of Mes* > Tip > Mes > phenyl.

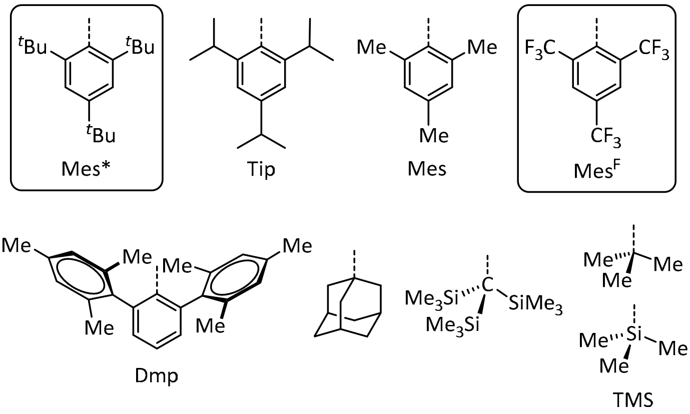


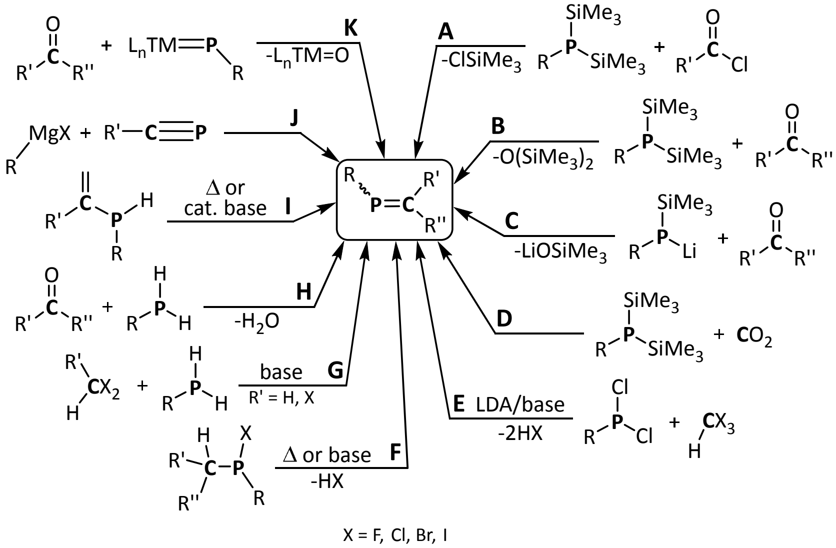
Figure 2.6 Molecular structures of commonly used bulky protecting groups for kinetic stabilization of phosphaalkenes.[77b]

Among the many examples, Mes* is probably one of the most established and popular protecting groups and is also used in the work of this thesis. This is mainly due to its steric shape and enormous bulkiness as well as convenient method for the preparation of the 2,4,6-tri(*tert*-butyl)bromobenzene (Mes*-Br) starting material on a multigram scale.[78]

Besides steric aspects, also electronic effects are useful in kinetic stabilization of low-valent P=C compounds.[77b] Particularly, bulky aromatic groups with strong electron-withdrawing moieties (e.g. CF_3) such as tris(trifluoromethyl)phenyl (Mes^F) (*Figure 2.6*), which is employed in this work as well, can significantly change the electronic properties and chemical reactivity of the corresponding phosphaalkenes. In combination with electron-rich protecting groups (e.g. bulky phenoxy or amino-containing groups) organophosphorus compounds with interesting push-pull type substitution are possible to synthesize.

2.2.3 Synthetic routes towards phosphaalkenes

The first phosphaalkene was synthesized in 1976 by BECKER *et al.* in a condensation reaction of bis(trimethylsilyl)phosphine with acyl chloride, followed by a 1,3-silyl shift (route **A** in *Scheme 2.11*).[79] Since then, there have been numerous reports of synthetic procedures for the formation of P=C bonds and low-valent organophosphorus compounds. *Scheme 2.11* presents an overview of some commonly used methods to prepare acyclic phosphaalkenes, and also here parallels to olefin syntheses are present.[58-59, 70a, 80]

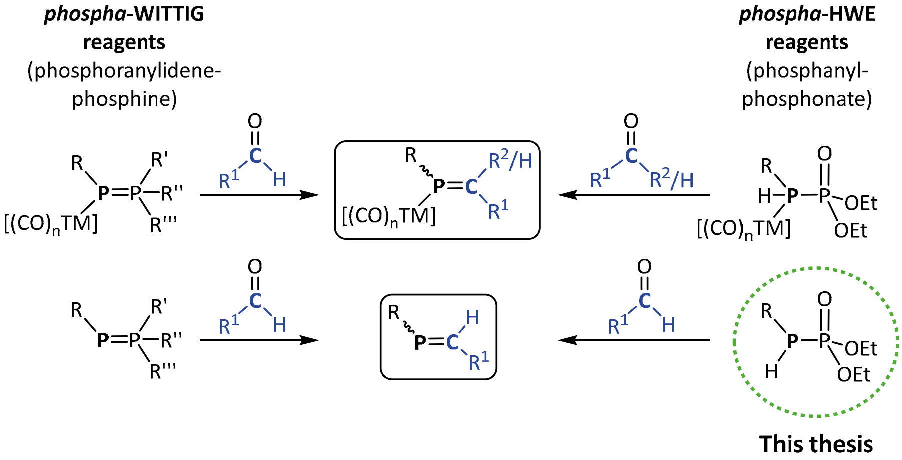


Scheme 2.11 General synthetic approaches towards phosphaalkenes.

The synthesis of the first stable phosphaalkene was a landmark, and this condensation reaction followed by 1,3-silatropic rearrangement still remains one of the most commonly used method (route **A**).[81] The *phospha*-PETERSON reaction constitutes a further reliable route.[82] Here, silicon-lithium activated phosphines undergo a condensation with an aldehyde, ketone or amide, and a subsequent 1,3-trimethylsilyl migration generates the energetically more stable phosphaalkene product (route **B** and **C**).[82-83] This reaction can also be mediated by a Lewis-acid such as $AlCl_3$.[84] The silatropic shift route is very general and can be combined with addition reactions of small molecules. For example, carbon dioxide, which exhibits cumulated hetero double bonds, can be inserted into the bis(TMS)phosphine leading to a phosphaalkene with two OTMS groups on the C-terminus (method **D** in *Scheme 2.11*).[85] A further main preparative procedure is the classical 1,2-elimination of HX (dehydrohalogenation) from appropriate precursors (route **E**, **F** and **G**).[80b, 86] This method was used for the synthesis of first phosphaalkenes without heteroatom substituents, reported by BICKELHAUPT *et al.* in 1978.[87] It is also an elegant approach towards *C*,*C*-dihalo substituted phosphaalkenes by treating *P*,*P*-dichlorophosphines, which are among the most common starting materials, with haloform or tetrahalomethane and a base (**E**).[88] Since this reaction is thermally initiated by a base (e.g. Et_3N, DBU, DABCO),[89] the halophosphines should contain a sufficiently acidic α-proton (**F**).[80b] Another variation is a direct carbene insertion with either CH_2X_2 or CHX_3 ($X = Cl, Br, I$) to primary phosphines in the presence of strong bases such as KOH (**G**).[86a, 86b, 86g] Alike imines, phosphaalkenes can be prepared by condensation of primary phosphines with suitable carbonyl derivatives (route **H**).[90] Moreover, this can also be performed in the presence of dehydration agents such as P_4O_{10} or $CaO/CaCl_2$.[81] In some cases, secondary vinylphosphines tend to equilibrate or thermally isomerize through a 1,3-proton shift (double bond migration) to the corresponding phosphaalkenes (**I**).[91] Phosphaalkynes, which are P-C triple bond containing compounds, can react with GRIGNARD reagents to form metal substituted phosphaalkenes after nucleophilic attack of R at the P-center (route **J**).[92] A further exchange of the metal by other electrophiles gives phosphaalkenes with desired substitution pattern. Finally, phosphaalkenes may also be obtained from the reaction of transition metal-terminal phosphinidene complexes with carbonyl compounds (method **K** in *Scheme 2.11*).[93] This can be referred to as a phosphorus version of the TEBBE olefination (compare *Scheme 2.2* in section 2.1.1). Important to mention is that in all presented methods from *Scheme 2.11* the phosphaalkenes can have coordination to a transition metal, if the phosphorus precursor is metal-coordinated.

Recent advances in the synthesis of phosphaalkenes are based on phosphorus variants of the classical WITTIG and HWE reactions (*Scheme 2.12*).[67, 94] This is another illustration of the analogy between phosphorus and carbon.[58b, 67] In the *phospha*-WITTIG variant a phosphoranylidenephosphine (*phospha*-ylide) reagent is reacted with aldehydes (but not ketones) to yield the corresponding phosphaalkenes in high yields. Initial work involved metal-coordinated (W, Mo, or Fe) *phospha*-WITTIG reagents in order to stabilize both the starting *phospha*-ylide and the final product.[95] Later, also metal-free *phos-*

pha-Wittig reagents were developed.[96] In the *phospha*-HWE variation the reagents contain a $(RO)_2P{=}O$ unit, and are more reactive so that also ketones can be used for the preparation of trisubstituted phosphaalkenes.[58b, 95a, 95d]



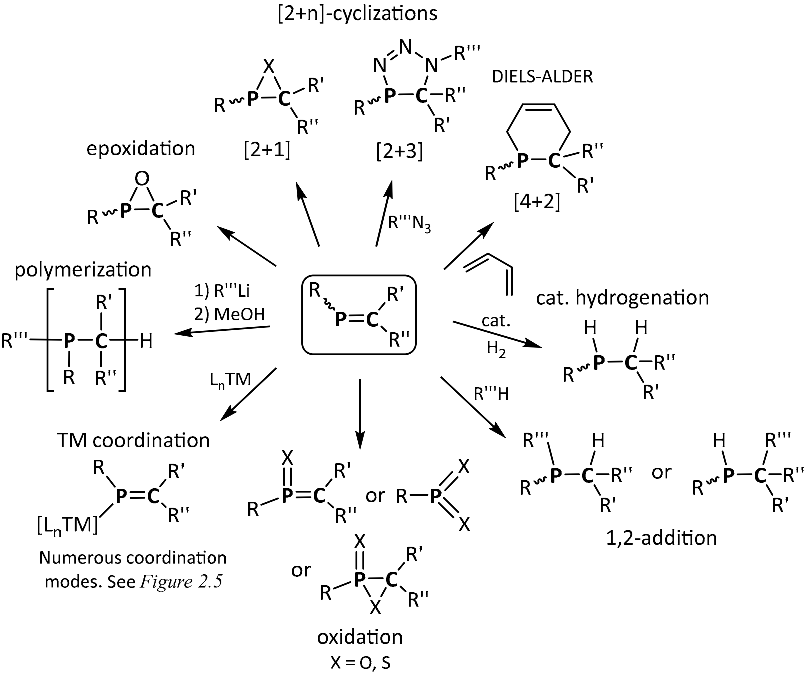
Scheme 2.12 Phosphorus variations of the WITTIG-type approach towards phosphaalkenes. *Left*: transition metal-coordinated (top) and metal-free (bottom) *phospha*-WITTIG reaction with aldehydes. *Right*: transition metal-coordinated (top) and metal-free (bottom) *phospha*-HWE reaction with aldehydes or ketones. R = PG = aryl (e.g. Mes* or Dmp), R′, R″, R‴ = aryl, alkyl; R^1, R^2 = aryl, alkyl, heteroaryl, *etc*.

Multi-gram syntheses for $W(CO)_5$-coordinated and metal-free *phospha*-HWE reagents and their use in the preparation of phosphaalkenes were recently reported by our group.[97] Especially, the metal-free *phospha*-HWE method is very important for this thesis and will be discussed in further chapters in more detail.

2.2.4 Reactivity and applications of phosphaalkenes

Phosphaalkenes show a wide reactivity which closely reflects that of olefins.[58b, 64a, 67] Thus, numerous standard reactions of the C=C unit such as 1,2-additions like hydrogenations or hydrohalogenations, epoxidations, oligo- and polymerizations, *E*/*Z* photoisomerizations,[98] oxidations, various [2+n]-cycloadditions, metal complexations, *etc*. have been successfully applied on phosphaalkenes.[58b, 59, 64a, 67, 70a, 70c, 73, 81, 94b] A general overview for the broad range of reactivity is depicted in *Scheme 2.13*. Some of the reactions in *Scheme 2.13* can be performed on transition metal coordinated phosphaalkenes, and such η^2 complexes or π-allyl complexes underline once more the close resemblance to olefins. Furthermore, additions with a number of 1,3-dipolar reagents and the phosphorus analog of DIELS-ALDER reactions are powerful methods to prepare new types of 5- and 6-membered, phosphorus-containing heterocycles.[99] Such cycloadditions follow in most cases the WOODWARD-

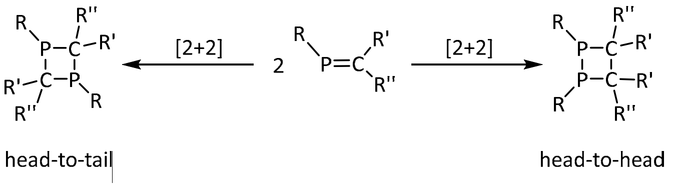
HOFFMANN rules.[59] In reactions with electrophiles there is often no distinction between the P=C bond and the lone pair due to the small energy gap between the phosphaalkene π and n_P orbitals.[67] This is the case for oxidations[100] and sulfurizations.[101] In addition to all the chemical transformations that can be performed on the P=C bond, there is also the possibility to functionalize phosphaalkenes at the peripheral substituents.[58a]



[2+n]-cyclizations
epoxidation
[2+1]
[2+3]
DIELS-ALDER
[4+2]
R'''N3
polymerization
1) R'''Li
2) MeOH
cat. hydrogenation
cat.
H2
R'''H
LnTM
TM coordination
Numerous coordination modes. See Figure 2.5
1,2-addition
or
oxidation
X = O, S

Scheme 2.13 Different types of reactivity of the P=C unit in phosphaalkenes.

In many cases, the reactions performed on phosphaalkenes require protection of the lone pair *via* coordination to a transition metal. If no stabilization is provided, phosphaalkenes tend to engage in self-addition reactions which lead to oligomerization or formation of [2+2] head-to-head or head-to-tail dimers (*Scheme 2.14*).[58b, 80a, 80b, 81, 82c, 102] This tendency increases with decreasing volume of the substituents. Head-to-head dimerization is typical for phosphaalkenes that carry bulky substituents at the phosphorus and small substituents at the carbon atoms and *vice versa*. This is a result of reduced intramolecular repulsions in the 1,2-diphosphetane cycles with long P-P and short C-C single bonds and *vice versa* compared to 1,3-diphosphetanes with four equal P-C bonds of intermediate length.[102a]



Scheme 2.14 [2+2]-cycloaddition (self-addition) of phosphaalkenes to either 1,2- or 1,3-diphosphetanes.

Interestingly, by proper choice of the substituents at the P- and C-atom the regioselectivity in reactions with polar reagents such as hydrogen halides, alcohols, amines, or thiols (1,2-additions) can be controlled.[80b, 99b] Here, we have to distinguish between normally or "*classically*" and inversely polarized phosphaalkenes which clearly differ in their chemical reactivity.[103] Usually, the phosphorus center has electrophilic properties and can be attacked by various nucleophiles, whereas inversely polarized phosphaalkenes are pronounced nucleophiles *via* their P-atom. This is demonstrated in the resonance structures in *Figure 2.7*. Therefore, reactions with protic reagents can lead to C-H (normal) or P-H (inverse) products depending upon the polarity of the P=C bond (see example in *Scheme 2.13*).[99b] The rate of such 1,2-additions generally decreases with increasing volume of the reagent and steric shielding of the P-C π-bond.[80b]

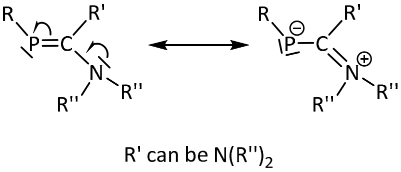


Figure 2.7 Resonance structures for phosphaalkenes with reverse electron density (inversely polarized).

As described above, the broad range of reactivity and the possibility to chemically modify the P=C unit enable utilization of phosphaalkenes in many different fields such as ligands and transition metal complexes in catalysis,[76c] monomeric building blocks in polymerization for phosphorus containing and π-conjugated polymeric materials.[70a, 70c, 104] For example, GATES and PROTASIEWICZ introduced various *phospha*-PPVs featuring P=C bonds in the main chain of the polymer by using *phospha*-WITTIG reactions and anionic initiations.[104a-c, 105] Applications as monodentate or chelating ligands have been reported in catalytic reactions such as hydro- and dehydrosilylations, hydroaminations, isomerizations, allylic substitutions, and cross-coupling reactions.[64a, 76c] Recently, phosphaalkenes were used as novel ligands for the stabilization of gold nanoparticles.[106] Another interesting field of application is in organic electronics. It has been shown that incorporation of phosphorus into the framework of π-conjugated organic molecules can alter the properties of the materials.[70b, 70d] Since phosphaalkenes have a smaller HOMO-LUMO gap compared to olefins it can be used to tune the optoelectronic features of a system. This makes phosphaalkenes valuable building blocks and potential materials for electronic devices such as semi-conductors, OLEDs, and photovoltaics.[107]

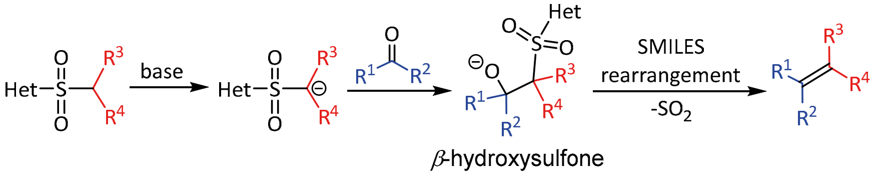
3. Novel methodology for aldehyde-aldehyde couplings *via* phosphaalkene intermediates (Paper I)

This chapter is dedicated to the development of a new methodology for an unprecedented reductive coupling of two different aldehydes to unsymmetrical *E*-alkenes using organophosphorus chemistry. The activation of phosphaalkene intermediates for carbonyl couplings, mechanistic investigations, optimization of the reaction conditions for the development of a one-pot procedure, and the investigation of the substrate scope are presented in detail. Finally, the advantages and drawbacks of the new method are discussed with respect to state-of-the-art olefination methods.

3.1 Alternative phosphorus-free aldehyde olefinations for 1,2-disubstituted *E*-alkenes

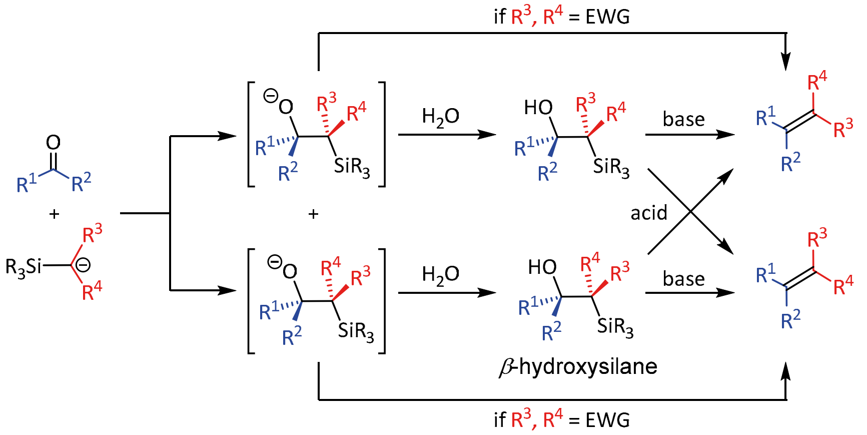
Many standard procedures for the preparation of 1,2-disubstituted alkenes are based on WITTIG-type chemistry and have been introduced in chapter 2.1. However, in the following some of the mentioned phosphorus-free (*non*-WITTIG) alternative olefination methods will be discussed more detailed. These are the commonly used JULIA and PETERSON reactions.

The classical JULIA-LYTHGOE reaction involves the coupling of aryl sulfones with aldehydes or ketones in two steps. First, a *β*-hydroxysulfone intermediate is generated which affords the alkene product after reductive elimination.[16, 108] Mechanistically, the reduction proceeds *via* a radical species and predominantly forms *E*-alkenes.[10a] The JULIA-KOCIENSKI variation is a one-pot procedure in which specially designed sulfones with heterocycles (Het) such as benzothiazole or 1-phenyl-1*H*-tetrazole allow an *in situ* reductive elimination *via* a SMILES-type rearrangement (*Scheme 3.1*). [109] In general, strong bases and stoichiometric quantities of reagents are required, but the reaction has a high substrate versatility and good functional group tolerance.



Scheme 3.1 JULIA-KOCIENSKI one-pot olefination.

The PETERSON olefination describes the reaction of *α*-silyl carbanions with aldehydes or ketones to form a mixture of diastereomeric *β*-hydroxysilanes, which provide alkenes after elimination of silanol.[10a, 15, 110] Generally, the *β*-silyl alcohols generated from *α*-silyl carbanions with electron withdrawing groups (EWG) are unstable, and undergo a spontaneous elimination to form *E*/*Z* product mixtures favoring the *E*-isomer. *β*-Silyl alcohols arising from *α*-silyl carbanions with electron donating groups (EDG) can be isolated and converted into the corresponding alkenes with a controlled stereochemistry.[111] Treatment of isolated and diastereomerically pure *β*-hydroxysilanes with base (e.g. NaH, KH, *t*-BuOK) results in *syn*-elimination, whereas treatment of the same substrate with dilute acid or a Lewis acid (e.g. AcOH, H_2SO_4, $BF_3{\cdot}OEt_2$) leads to *anti*-elimination (*Scheme 3.2*).[112] Hence, the stereoselectivity depends on the availability of diasteriomerically pure *β*-hydroxysilane intermediates.

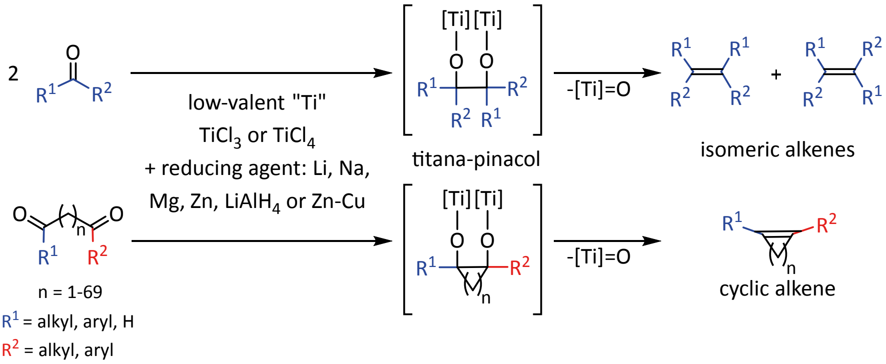


Scheme 3.2 The PETERSON reaction under basic and acidic conditions.[113]

In comparison to the WITTIG reaction, PETERSON reagents are more reactive than phosphorus ylides due to the higher nucleophilicity of *α*-silyl carbanions, and the disiloxane by-products are easier to remove.[15b, 113-114] However, the low synthetic availability of certain *α*-silyl carbanions limits its general use.[115]

3.2 Direct carbonyl-carbonyl couplings to olefins – the McMurry reaction

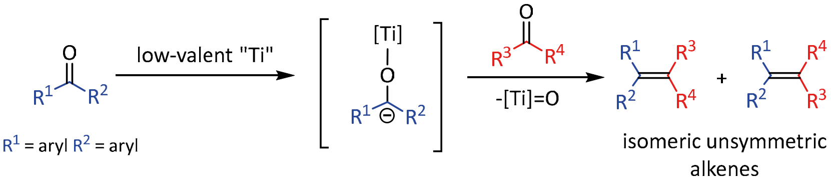
In 1974 McMurry reported on the reductive coupling of carbonyls to form olefins using $TiCl_3$ and $LiAlH_4$.[24a] During the last few decades, this coupling gained much interest in organic synthesis and has been utilized in a broad range of applications.[10a, 11, 24c, 116] In most cases, it is used for the intermolecular homo-couplings of two aldehydes or ketones or in an intramolecular fashion to form macrocycles. The reaction proceeds *via* titanapinacol intermediates and a radical mechanism (*Scheme 3.3*).[24c] As outlined in section 2.1.1, this method is less applicable to preparations of unsymmetrical alkenes by cross-couplings since usually a mixture of symmetrical and unsymmetrical products is generated (*Scheme 2.3*).



Scheme 3.3 General representation of the "low-valent" Ti^0 promoted intermolecular homo-coupling (top) and intramolecular coupling of two carbonyls under ring formation (bottom).[10a]

In general, the reaction has poor stereoselectivity and the *E*-isomer is favored over the *Z*-isomer, although mixtures may result when the substituents have similar steric demand. The driving force of the reaction is the formation of strong titanium-oxygen bonds, and the reactivity of the active Ti^0 species strongly depends on its method of preparation. Even solvent effects can be crucial in the stabilization of the zero-valent titanium particles. However, the most common approach is the reduction of $TiCl_3$ with a zinc-copper mixture in DME.[116a] Although this reaction has a broad scope, functional groups that are prone to reduction are incompatible. These are for example allylic and benzylic alcohols,[117] unprotected 1,2-diols,[116a] epoxides,[118] nitro compounds,[119] oximes,[120] and sulfides.[121]

Due to the lack of substrate selectivity, unsymmetrical olefins are challenging to obtain from McMurry reactions. One notable exception is when one of the carbonyl coupling partners is a diaryl ketone, as the rapid two electron reduction of that carbonyl provides a stable titanium ketyl anion.[122] This anion then adds to the saturated ketone or aldehyde by a nucleophilic addition mechanism to yield a mixed pinacol product, which after deoxygenation by titanium affords an unsymmetrical alkene (*Scheme 3.4*).[24b] Another strategy to obtain unsymmetrical olefins is to use one component in excess.[116a]

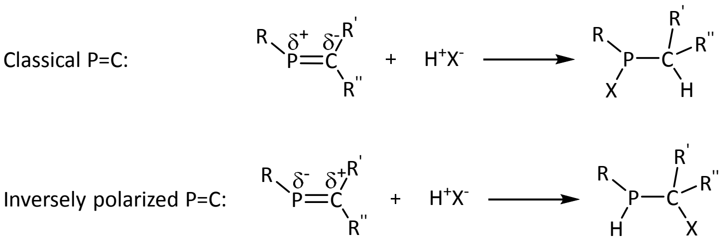


Scheme 3.4 MCMURRY cross-coupling with diaryl ketones.[122]

To conclude, the MCMURRY reaction is a powerful method for the dimerization of two carbonyls to symmetrical alkenes.[123] However, due to difficulties in the preparation of the active Ti^0 species, intolerance of easily reduced functional groups, and bad reproducibility of yields, this reaction is often described as "*tricky*".[10a]

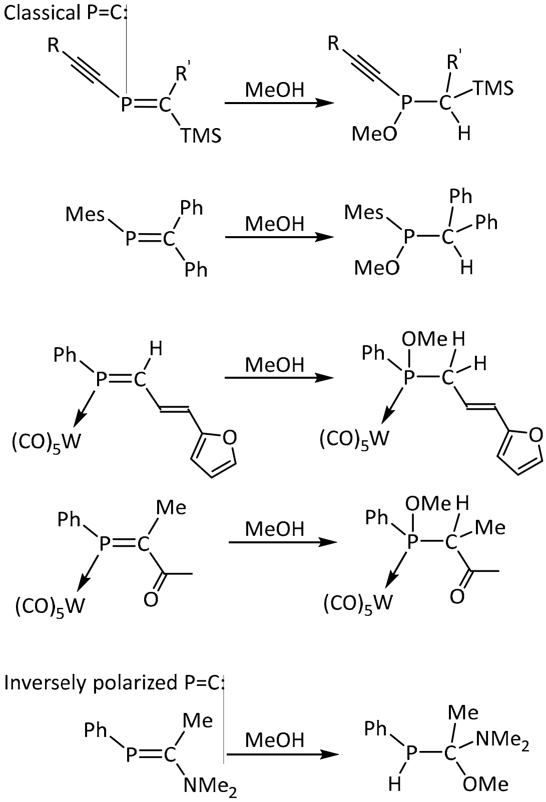
3.3 Phosphaalkenes in the role of electrophiles

As discussed in section 2.2, phosphaalkenes have a polarized double bond due to the difference in electronegativity between the C- and P-atom (2.5 and 2.1, respectively) in the direction of $C^{\delta-}P^{\delta+}$.[58b, 59, 67, 80b] The exact distribution of π-electron density is influenced by the substituents on the carbon and phosphorus atoms.[104e] In "*classical*" phosphaalkenes the phosphorus center of the P=C bond has electrophilic character and is prone to nucleophilic attack. There are many different examples of nucleophilic reactions in the literature. In the case of protic reagents (e.g. hydrogen halides, alcohols, amines, or thiols), the X-H bond adds across the P=C double bond to give a protonated carbon center and the nucleophile at the phosphorus atom.[80a, 80b, 124] Depending on the type of substituents on the carbon center of the phosphaalkenes, the polarization of the double bond can be inversed leading to $C^{\delta+}P^{\delta-}$.[103] For such species an opposite regioselectivity for the addition of a proton donor reagent is observed (see *Scheme 3.5* and in comparison with *Scheme 2.13*).[99b]


Classical P=C:
Inversely polarized P=C:
δ+
δ-
H+X-

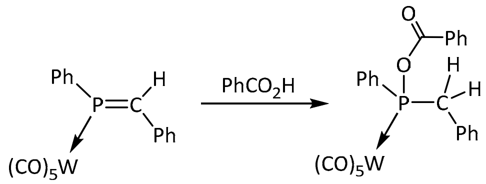
Scheme 3.5 General reactivity behaviour of proton active reagent towards different types of phosphaalkenes.[80b]

A common reaction of phosphaalkenes is trapping with methanol which generates the corresponding phosphinites. Some selected examples are shown below in *Scheme 3.6*.[87, 95b, 95d, 99b, 125]


Classical P=C:
MeOH
Inversely polarized P=C:

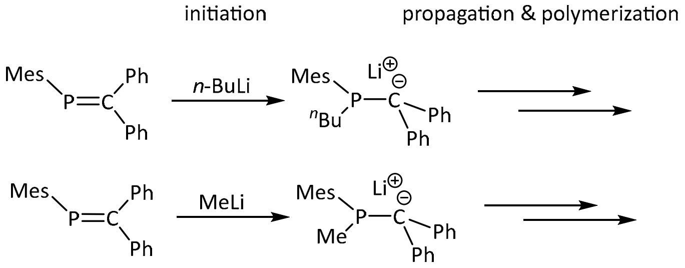
Scheme 3.6 Selected examples for trapping of phosphaalkenes by methanol. Reaction with classical (top) and inversely polarized (bottom) phosphaalkenes.

A further interesting example is the base-catalyzed reaction of benzoic acid with the P=C bond.[95b] Here, benzoate acts as nucleophile and attacks the phosphorus center leading to formation of P-O and C-H bonds (*Scheme 3.7*).


PhCO$_2$H
(CO)$_5$W
(CO)$_5$W

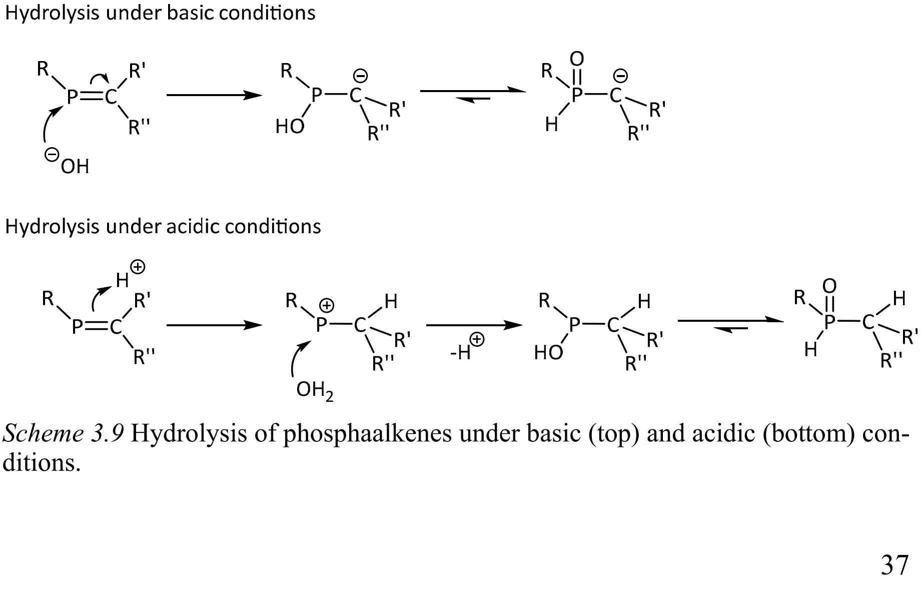
Scheme 3.7 Trapping of phosphaalkenes with benzoic acid.[95b]

Due to the electrophilicity of the P=C bond, phosphaalkenes are interesting and important building blocks in polymerization reactions. GATES *et al.* used this characteristic to activate the P=C bond by addition of *n*-BuLi or MeLi as initiators for anionic polymerizations. The resulting carbanion can react with another P=C monomer and initiate a propagation at mild reaction conditions (*Scheme 3.8*).[70c, 105, 126]


initiation
propagation & polymerization
n-BuLi
MeLi

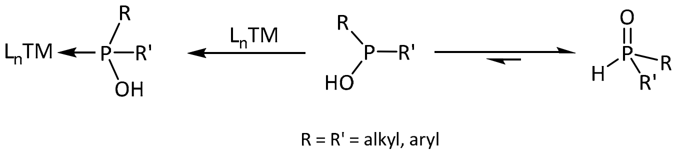
Scheme 3.8 Examples of anionic polymerization of phosphaalkenes initiated by nucleophilic attack by *n*-BuLi or MeLi.

The instability of phosphaalkenes towards moisture is a very well known phenomenon. In fact, hydrolysis of phosphaalkenes is another example of the electrophilic character of the P=C bond (see in *Scheme 3.9*).


Hydrolysis under basic conditions
Hydrolysis under acidic conditions
-H⊕

Scheme 3.9 Hydrolysis of phosphaalkenes under basic (top) and acidic (bottom) conditions.

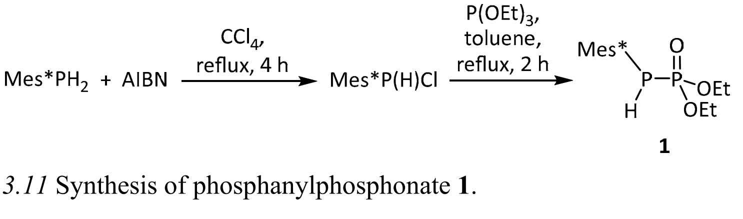
If the kinetic stabilization is insufficient, hydrolysis can take place either under basic[127] or acidic[128] conditions, and lead to the corresponding secondary phosphine oxide (SPO) product as depicted in *Scheme 3.9*. The hydrolysis of phosphaalkenes is accompanied by the tautomerization of the phosphinous acid (P^{III} species) to the corresponding SPO (P^{V} species). The equilibrium between the pentavalent SPO and the trivalent phosphinous acid lies mostly towards the formation of the SPO for R = R` = alkyl or aryl (*Scheme 3.10*).[129] Under ambient conditions the air-stable P^{V} tautomer is usually predominant. In order to stabilize the disfavored phosphinous acid, strongly electron-withdrawing substituents, such as trifuoromethyl, pentafluoroethyl and perfluoroaryl groups, are necessary.[130] Another strategy to stabilize the P^{III} tautomer is coordination of the free electron pair with a metal center.[131] A general tautomeric equilibrium is shown in *Scheme 3.10*.[132]



Scheme 3.10 Tautomerism between the trivalent phosphinous acid and pentavalent secondary phosphine oxide and the formation of metal complexes with the P^{III} tautomer.

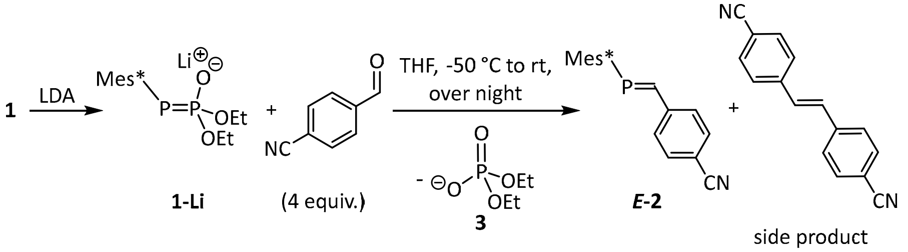
3.4 Coupling reagent – preparation and application in the synthesis of phosphaalkenes

The synthesis of the first *phospha*-HWE reagent, a metal-free and bench stable compound, was developed in our group and used in the preparation of metal-free phosphaalkenes.[97b] Kinetic stabilization of the phosphaalkenes is provided by the bulky Mes*-group. The synthesis of the phosphanylphosphonate **1** can be performed on a multigram scale in two steps from Mes*PH_2.[78, 133] Mes*PH_2 can undergo monochlorination with CCl_4 and AIBN under a radical mechanism to afford the secondary phosphine Mes*PHCl.[134] This intermediate can be directly converted to the phosphanylphosphonate **1** in a *phospha*-MICHAELIS-ARBUZOV reaction. The synthesis is outlined in *Scheme 3.11*.



Scheme 3.11 Synthesis of phosphanylphosphonate **1**.

As mentioned above, the deprotonated form of compound **1** (*phospha*-enolate **1-Li**) can react with aldehydes in a *phospha*-HWE reaction to yield phosphaalkenes. This reaction has a broad substrate scope, exhibiting reactivity with aliphatic, aromatic, vinylic and heterocyclic aldehydes.[97b] When this reagent was used in the reaction with 4-cyanobenzaldehyde, a blue fluorescent side-product was formed. After isolation in 5% yield, it was characterized as the homo-coupled olefin (*E*)-4,4'-(ethene-1,2-diyl)dibenzonitrile (*Scheme 3.12*).



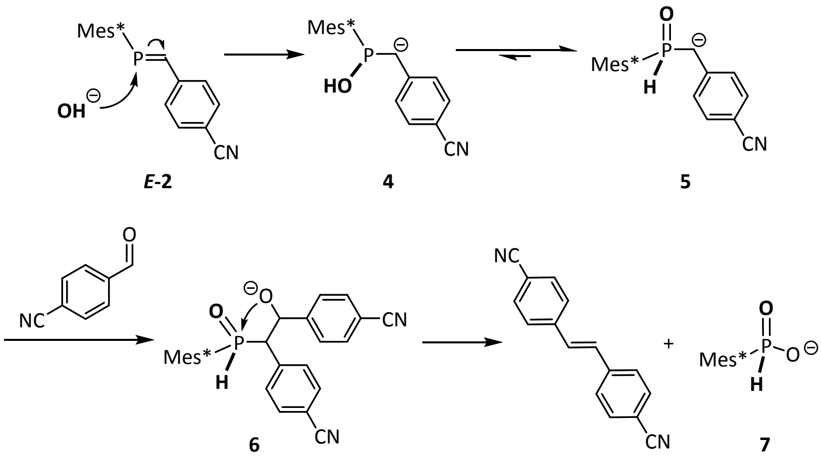
Scheme 3.12 Synthesis of phosphaalkene ***E*-2** from the reaction of phosphanylphosphonate **1** with an aldehyde and formation of the olefinic side-product.

The unexpected alkene formation strongly attracted our attention, and gave rise to in depth mechanistic investigations regarding the formation of an alkene from a phosphaalkene under basic conditions and in the presence of excess aldehyde. These investigations led to the development of the new methodology for the synthesis of *E*-alkenes by the reductive coupling of aldehydes.

3.5 Optimization of reaction conditions

3.5.1 Mechanistic investigations by NMR studies

Our hypothesis for the formation of the olefinic side-product from the phosphaalkene is associated to the basic conditions under which the *phospha*-HWE reaction is performed and worked-up. Considering the electrophilic character of the P=C bond, an attack at the P center by a nucleophile such as hydroxide can be envisaged. Reaction of the phosphaalkene ***E*-2** with hydroxide from adventitious water would result in the formation of phosphinite **4**, leading to the SPO **5** by tautomerization, which is comparable to a HW olefinating reagent. Compound **5** would then be able to react with another equivalent of aldehyde to produce the stilbene and the phosphinate **7**, identifiable by ^{31}P NMR spectroscopy. A schematic picture of our proposed mechanism is shown in *Scheme 3.13*.



Scheme 3.13 Proposed mechanism for alkene formation from phosphaalkene ***E*-2**. Nucleophilic attack by hydroxide on the P=C bond leads to hydrolysis of ***E*-2** and tautomerism to the corresponding SPO carbanion **5** which upon reaction with aldehyde conducts the sequence to alkene formation.

In order to validate our hypothesis and the proposed mechanism, the reaction was monitored by ^{31}P NMR spectroscopy. Since it is a very suitable technique to follow each transformation, a detailed mechanistic picture can be revealed. NMR tube experiments were performed on the hydrolysis of isolated phosphaalkene ***E*-2** with NaOH as base and wet THF as solvent (*Figure 3.1*). The reaction was slow but after 2-3 days all phosphaalkene was fully consumed and in the ^{31}P NMR spectrum a new peak at 25 ppm as the only signal was observed (*Figure 3.1*, b → c). This peak was assigned to the SPO **5-H**. Addition of 4-cyanobenzaldehyde at this point consumes most of the SPO overnight and the final phosphinate by-product **7** can be detected as the main signal at 15 ppm (*Figure 3.1*, c → d).

Under the given reaction conditions two equilibria are assumed to be present (*Figure 3.1*, a). The first equilibrium is the tautomerism between phosphinous acid **4-H** and SPO **5-H**. Under ambient conditions and at room temperature SPO formation is favored. The second equilibrium is an acid/base equilibrium between the protonated and deprotonated form of the phosphine oxide (**5-H** and **5**, respectively). Proton coupled ^{31}P NMR (C_6D_6) spectroscopy reveals the singlet at 25 ppm to be actually a doublet of triplets with two types of couplings: $^{1}J_{\text{P-H}} = 498$ Hz for the directly attached proton, and $^{2}J_{\text{P-H}} = 17$ Hz for the protons at the α-carbon (*Figure 3.1*, c). The chemical shift and the coupling constants are in agreement with similar compounds such as Mes*P(O)HCH$_2$Ph (CDCl$_3$, $\delta_{31\text{P}} = 28$ ppm, $^{1}J_{\text{P-H}} = 495$ Hz and $^{2}J_{\text{P-H}} = 15$ Hz) reported by YOSHIFUJI *et al.*[135] The splitting pattern suggests that the predominant species is **5-H** rather than its conjugate base **5**. However, the equilibrium is shifted towards deprotonated form of SPO **5** upon addition of 4-

cyanobenzaldehyde, driving the conversion of **5** to **7** (*Figure 3.1*, c → d). After aqueous work-up, 2,4,6-tri-*tert*-butylphenyl phosphinic acid **7-H** was isolated as colorless solid. Isolation of **7-H** gives further support for the accuracy of our hypothesis regarding the ionic mechanism and the reaction sequence. Phosphinic acid **7-H** shows a characteristic doublet at 27 ppm in the proton coupled ^{31}P NMR spectrum with a coupling constant of $^{1}J_{\text{P-H}} = 576$ Hz. The corresponding coupling constant and a very large doublet at 8.16 ppm was also observed in the ^{1}H NMR spectrum of this compound.

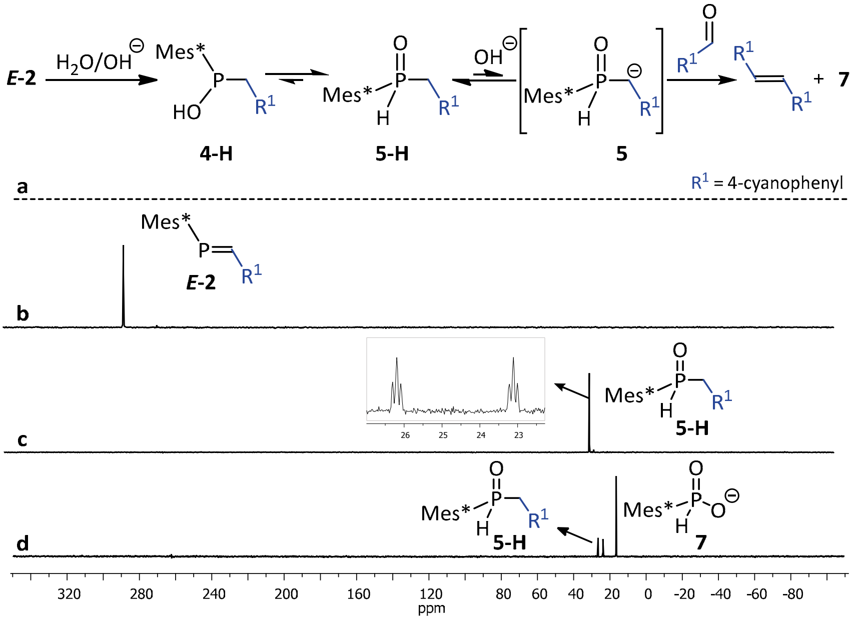


Figure 3.1 ^{31}P NMR monitoring of the hydrolysis of phosphaalkene by NaOH$_{aq}$ to phosphine oxide **5-H** and the formation of the phosphinate by-product **7** after reaction with aldehyde.

Secondary phosphine oxide **5-H** could be prepared on a 500 mg scale by hydrolysis of phosphaalkene ***E*-2** at room temperature within 14 days with NaOH in degassed THF and a small amount of water. After isolation, crystals suitable for X-ray diffraction were obtained by slow evaporation from *n*-hexane. Compound **5-H** crystalizes in the triclinic P -1 space group as colorless blocks. The solid state structure is represented in *Figure 3.2*.

Due to restricted rotation around the Mes*-P bond (P1-C9 bond), the ^{1}H NMR spectrum is temperature dependent. The aromatic protons of Mes* and the *ortho* methyl groups show either separate singlet signals, coalescence or signal broadening at corresponding temperatures.

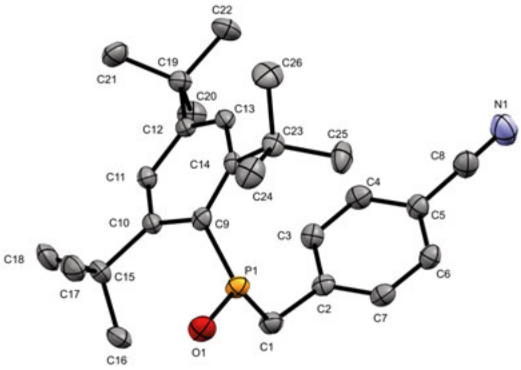


Figure 3.2 ORTEP plot of phosphine oxide **5-H** (with R^1 = 4-cyanophenyl) at 50% probability ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond length [Å] and angles [°]: P1-C1 1.835(2) Å, P1-C9 1.819(2) Å, P1-O1 1.4846(16), C1-P1-C9: 103.38(9) °.

In order to confirm that SPO **5-H** is a true intermediate in the reaction, it was reacted with 4-cyanobenzaldehyde and tetrabutylammonium hydroxide ($TBAOH_{aq}$) as the base at room temperature. Immediate formation of the corresponding stilbene product was observed.

It was found that the tautomerism between phosphinite **4** and phosphine oxide **5** is temperature dependent. The reaction between phosphaalkene ***E*-2** and $TBAOH_{aq}$ in the absence of an aldehyde can be monitored by ^{31}P VT-NMR spectroscopy (*Figure 3.3*). In an NMR tube 2 equivalents of $TBAOH_{aq}$ were added to ***E*-2** in THF at -80 °C, and the mixture was monitored by proton coupled ^{31}P NMR spectroscopy in the range -80 °C to 20 °C in 20 degree increments. *Figure 3.3* outlines the monitoring process. The equilibrium is strongly temperature dependent and at low temperatures (-80 °C) favors the phosphinite **4** while SPO **5** is favored at higher temperatures and room temperature (20 °C). The singlet at 109 ppm, which is present at temperatures below 0 °C, is assigned to the phosphinite since its chemical shift value is in the range for similar compounds like PPh_2OMe (115.6 ppm).[136] The formation of each tautomer is reversible and can be controlled by the choice of the temperature. At this point, one should mention that during the hydrolysis of phosphaalkene with $TBAOH_{aq}$ some side-products are formed if no aldehyde is present in the reaction mixture. This is confirmed by the presence of several signals in the ^{31}P NMR spectrum between 10 and 20 ppm (see *Figure 3.3*).

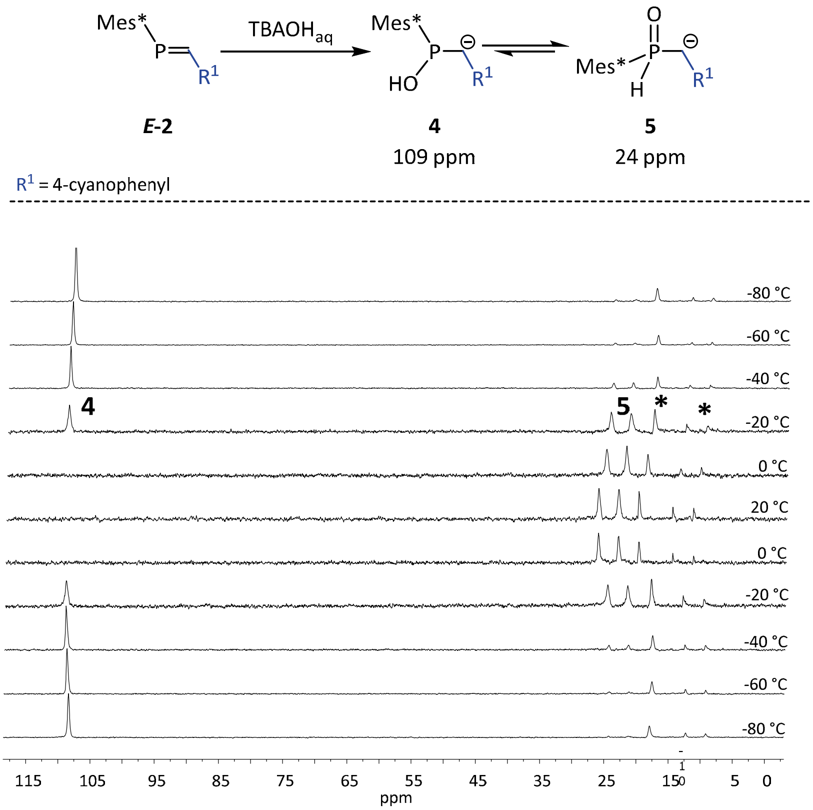


Figure 3.3 Variable temperature proton coupled ^{31}P NMR spectroscopic investigation of the hydrolysis of phosphaalkene ***E*-2** by TBAOH$_{aq}$ and the subsequent tautomerism between phosphinite **4** and phosphine oxide **5**. No aldehyde was added. *Unidentified decomposition products.

3.5.2 Influence of the base

The base is a key component to the synthetic procedure and, as such, essential for the initiation of the reaction with the second aldehyde. In general, any kind of base can be used in combination with catalytic amount of water. From the screening of different types of bases hydroxides were found to be most suitable. Herein, the source of hydroxide may be a metal hydroxide, such as NaOH, KOH or LiOH; or a hydroxide with an organic counter cation, such as tetrabutylammonium hydroxide (TBAOH$_{aq}$). Several hydroxide salts were tested with the aim to shorten the reaction times for the hydrolysis of phosphaalkene ***E*-2**. The results are summarized in *Table 3.1*.

Table 3.1 Different sources of hydroxide base and corresponding reaction times for the hydrolysis of phosphaalkene ***E*-2**.

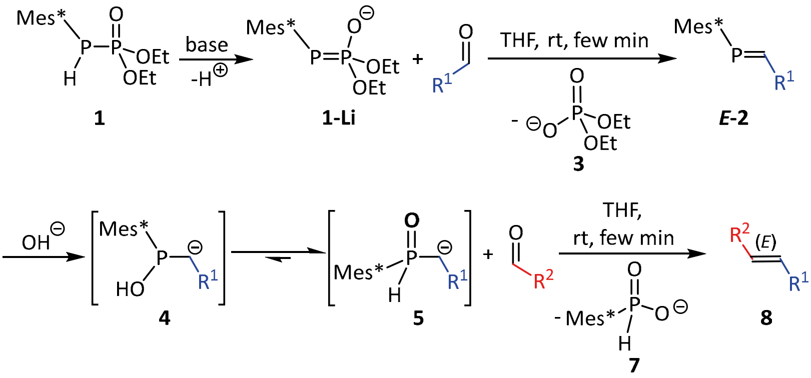
Base	**Full P=C consumption**
NaOH/H_2O	2 days
KOH/H_2O	2 days
Cs_2CO_3/H_2O	No reaction
CsOH/H_2O	Overnight
KOH/18-crown-6	Overnight
Bu_4NOH_{aq} (40%)	Immediate

Bases with low solubility in THF (e.g. NaOH, KOH, Cs_2CO_3) showed little reactivity with phosphaalkene ***E*-2**. Increasing the solubility of the base by incorporating crown ether or using CsOH resulted in a slight increase in reactivity with consumptions of ***E*-2** overnight. A dramatic change occurred when an aqueous solution of tetrabutylammonium hydroxide ($TBAOH_{aq}$) was used. Upon addition, an immediate color change was observed and the reaction was complete after few seconds. The large improvement in reaction time can be attributed to the ability of $TBAOH_{aq}$ to act simultaneously as a base and phase transfer catalyst. Another benefit of $TBAOH_{aq}$ is that it is inexpensive and commercially available as a 40 weight% solution. When the hydrolysis of ***E*-2** in presence of 4-cyanobenzaldehyde was followed by ^{31}P NMR spectroscopy, a new resonance at 12 ppm emerged. This new resonance is comparable to that of Mes*-phosphinate **7** upon reaction with NaOH (*Figure 3.1*), and is attributed to the analog of **7** with a TBA cation.

3.5.3 Development of a one-pot procedure

With the optimized reaction conditions and the proof that phosphaalkene ***E*-2** hydrolyses to SPO **5**, undergoing a HORNER-WITTIG-type olefination with a second aldehyde, all requirements were set for a one-pot reaction.

To this end, we aimed to couple directly *two* aldehydes under reductive conditions by synthesising ***E*-2** *via* a *phospha*-HWE reaction and a subsequent *in situ* hydrolysis. The hydrolysed species, SPO **5**, is expected to react with 4-cyanobenzaldehyde under the basic conditions in order to furnish the alkene product **8** (*Scheme 3.14*). Thus, in such a one-pot protocol the phosphaalkene is a true intermediate. Important to mention at this point is that the formation of phosphaalkene is concominant with a change in polarity (Umpolung) of the carbonyl carbon center from δ^+ to δ^-.



Scheme 3.14 General representation of the one-pot reductive coupling of two aldehydes to *E*-alkenes. For mechanistic studies $R^1 = R^2$ = 4-cyanophenyl.

The entire sequence of the one-pot procedure can be monitored conveniently by ^{31}P NMR spectroscopy (see *Figure 3.4*). Deprotonation of **1** by LDA leads to a characteristic shift of the two doublets at -90 and 34 ppm ($^1J_{P\text{-}P}$ = 222 Hz) to -119 and 69 ppm ($^1J_{P\text{-}P}$ = 615 Hz) for **1** and **1-Li**, respectively. Addition of one equivalent of aldehyde (4-cyanobenzaldehyde) yields the phosphaalkene ***E*-2** (resonance at 284 ppm) and the diethyl phosphate by-product **3** (resonance at 1 ppm). Addition of $TBAOH_{aq}$ and a second equivalent of the same aldehyde at this point results in the full consumption of ***E*-2**, as evidenced by the emergence of a new resonance at 12 ppm that stems from the Mes*-phosphinate **7** which is left behind after formation of the alkene product (not visible in ^{31}P NMR spectrum). Upon aqueous work-up the desired alkene product was isolated in high yields demonstrating the viability of the one-pot synthetic protocol. The convenient reaction monitoring by ^{31}P NMR spectroscopy gives direct evidence for the high conversions in each single step of the entire coupling reaction.

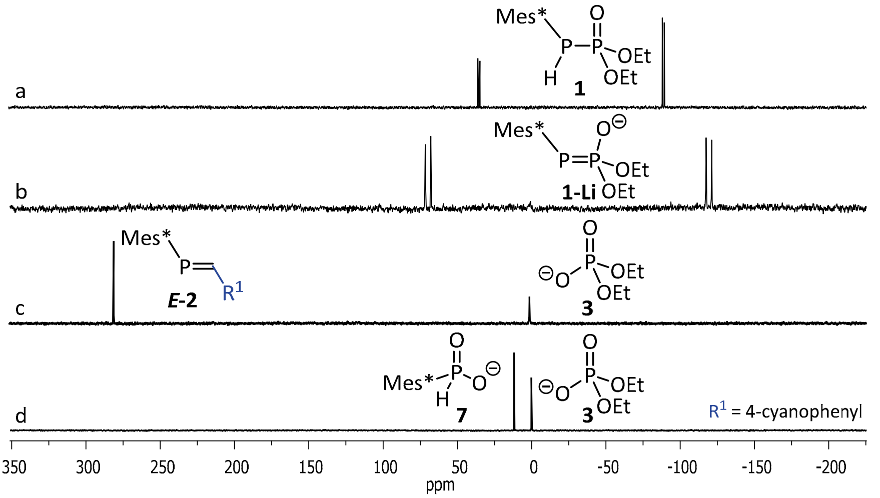


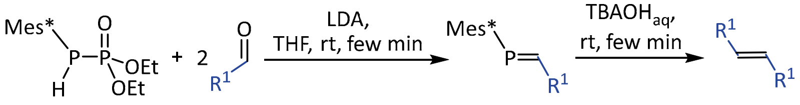
Figure 3.4 Step by step reaction monitoring by ^{31}P NMR spectroscopy. (a → b) Lithiation of phosphanylphosphonate **1** to **1-Li**. (b → c) *Phospha*-HWE reaction of **1-Li** with 4-cyanobenzaldehyde to form phosphaalkene ***E*-2** and diethyl phosphate by-product **3**. (c → d) Last step is the conversion of the phosphaalkene ***E*-2** to the alkene product after addition of $TBAOH_{aq}$ and subsequent reaction of the *in situ* formed SPO **5** with second equivalent of aldehyde. Mes*-phosphinate **7** is formed as by-product.

Furthermore, the addition of two equivalents of 4-cyanobenzaldehyde to **1-Li** from the beginning of the coupling sequence leads to the same reaction outcome. Hence, the persistence of the second equivalent of aldehyde until it reacts with the deprotonated SPO **5**, as soon as the latter is formed, allows a more simplified practical procedure for the homo-coupling of *two identical* aldehydes.

3.6 Substrate scope

With an optimized one-pot protocol in hand, the scope of the new aldehyde coupling reaction was investigated. Both the synthesis of symmetrical alkenes (homo-coupling) and unsymmetrical alkenes (cross-coupling) were investigated.

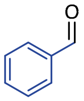
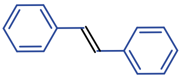
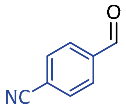
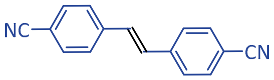
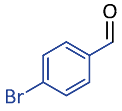
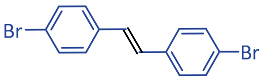
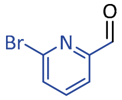
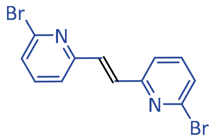
3.6.1 Symmetrical *E*-alkenes from homo-couplings



1 ***E*-2**

In a series of homo-couplings, two equivalents of several different benzaldehydes were added to a solution of **1-Li** in order to synthesize the corresponding stilbenes. The results of these couplings are summarized in *Table 3.2*. The reaction of unsubstituted benzaldehyde with **1-Li** afforded a clean formation of Mes*P=C(*Ph*)H which was confirmed by ^{31}P NMR spectroscopy and the appearance of the corresponding signal at 258 ppm. Addition of TBAOH$_{aq}$ consumed the phosphaalkene, and in about 45 minutes the stilbene product was formed. Although the isolated yield of 37% is moderate, it is important to realize that this is the first example of a reductive coupling of two benzaldehyde molecules under an ionic mechanism and at room temperature. Moreover, the consumption of Mes*P=C(*Ph*)H is within reasonably short time, but longer in comparison to the consumption of ***E*-2**. The reason for that is most likely the high electron-deficiency in the latter and the fact that electron-poor systems react much better in HW-type olefinations.

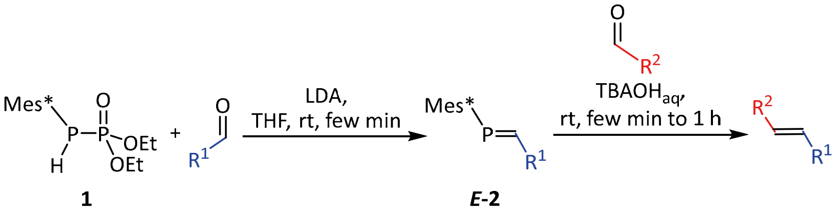
Table 3.2 Symmetrical *E*-alkene products from homo-couplings of two identical aldehydes.

Entry	Aldehyde	Product	Conversion (Isolated yield) [%]
1			(37)
2			>80 (75)
3			82 (50)
4			80

Consequently, we investigated electron-deficient aldehydes as substrates. The coupling of 4-bromobenzaldehyde gave a high conversion of 82% for the corresponding alkene (see *Table 3.2*). This also shows that halides are tolerated as functional groups. The electron-poor heterocyclic aldehyde, 6-bromo-2-pyridinecarboxaldehyde, was also tested, affording the homo-coupling product in a high conversion of 80%.

A trial to couple electron-rich trimethylacetaldehyde was unsuccessful. The P=C bond in Mes*P=C(*ᵗBu*)H is stable towards hydrolysis by TBAOH$_{aq}$. The inertness of this phosphaalkene may result from steric rather than electronic effects. Since the P=C bond is sterically protected by a large Mes*-group on the phosphorus side and by a bulky *tert*-butyl moiety on the carbon side, a nucleophilic attack by hydroxide is most probably hindered.

3.6.2 Unsymmetrical *E*-alkenes from cross-couplings

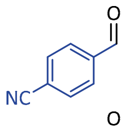
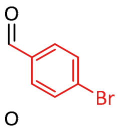
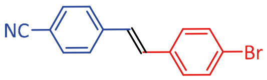
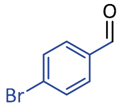
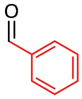
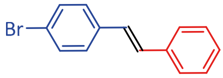
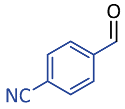
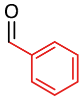
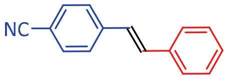
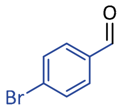
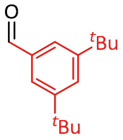
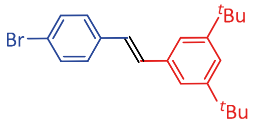
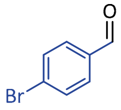
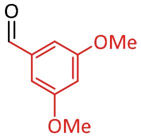
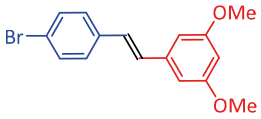


The possibility to couple selectively two *different* aldehydes is the most important feature in our newly developed methodology. This is a significant improvement compared to the MCMURRY coupling, where unsymmetrical products are obtained as a mixture with the corresponding symmetrical alkenes. The applicability of our method was tested in cross-couplings of a diverse selection of aldehydes. The results for all tested aldehydes are summarized in *Table 3.3* to *3.5*.

As discussed in section 3.6.1, electron-deficient aldehydes give high conversions in the reaction of phosphaalkenes to symmetrical olefins. Thus, 4-cyano-, 4-bromobenzaldehyde, and pyridine-based aldehyde were used for the first part of the coupling sequence, i.e. the *phospha*-HWE reaction. The *in situ* generated phosphaalkenes were obtained quantitatively and subjected to hydrolysis with TBAOH$_{aq}$ in the presence of an equivalent of a different aldehyde. In most cases good to very good conversions to the unsymmetrical *E*-alkenes were observed which gives a satisfying overall result for the novel methodology.

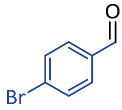
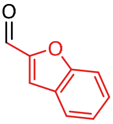
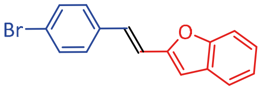
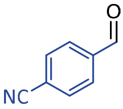
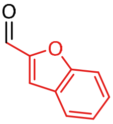
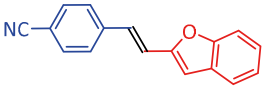
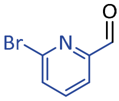
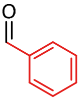
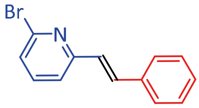
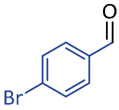
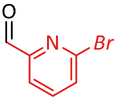
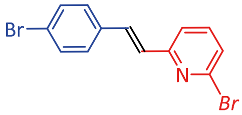
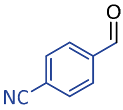
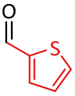
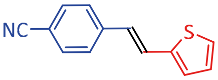
In all experiments described herein, no traces of the corresponding *Z*-isomers or the symmetrical homo-coupling products were detected. The highest conversion of 91% was obtained for the coupling of two electron-deficient aldehydes, namely 4-cyanobenzaldehyde with 4-bromobenzaldehyde (*Table 3.3*, Entry 1). If unsubstituted benzaldehyde was used as the second aldehyde, the conversions dropped to about 56-57% (*Table 3.3*, Entries 2 and 3). Reaction of benzaldehydes with bulky *tert*-butyl or electron-rich methoxy substituents in *meta*-position, such as 3,5-di-*tert*-butylbenzaldehyde and 3,5-dimethoxybenzaldehyde, resulted in very good conversions of 58% and 74%, respectively (*Table 3.3*, Entries 4 and 5). Interestingly, the 3,5-dimethoxybenzaldehyde showed a high conversion despite being electron-rich. This can be explained with the fact that the methoxy groups in *meta*-position cannot contribute to resonance, and hence are unable to push electron density towards the carbonyl group. Additionally, the present electron-pulling inductive effect of the methoxy substituents make the system electron-deficient which might be the reason for the high conversion.

Table 3.3 Unsymmetrical *E*-alkenes from cross-couplings of two different benzaldehydes.

Entry	**1st Aldehyde**	**2nd Aldehyde**	**Product**	**Conversion (Isolated yield) [%]**
1				91 (72)
2				56 (47)
3				57
4				58
5				74

In the next series of couplings, heterocyclic carboxaldehydes, such as benzofuran-, pyridine-, and thiophenecarboxaldehyde, were tested as the second coupling partner (see all results in *Table 3.4*). These aldehydes showed moderate to good conversions to the corresponding alkenes. The highest conversions of 68% and 50% were achieved with 2-benzofurancarboxaldehyde when coupled with 4-cyano- and 4-bromobenzaldehyde, respectively (*Table 3.4*, Entries 1 and 2). 6-Bromo-2-pyridinecarboxaldehyde gave the corresponding coupling products as well, albeit with reduced conversions (compare Entries 3 and 4 in *Table 3.4*). The method is also applicable to aldehydes with fivemembered heterocycles like 2-thiophenecarboxaldehyde which resulted in a successful coupling with a conversion of 44% (*Table 3.4*, Entry 5).

Table 3.4 Unsymmetrical *E*-alkenes from cross-couplings of benzaldehydes with heterocyclic carboxaldehydes.

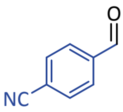
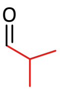
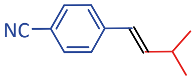
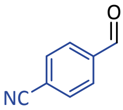
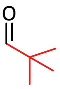
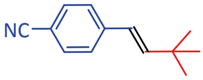
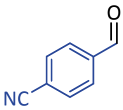
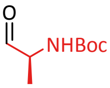
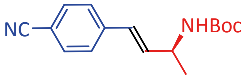
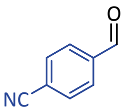
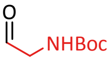
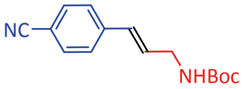
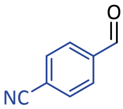
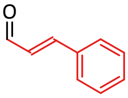
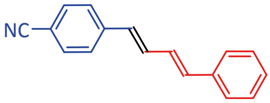
Entry	**1st Aldehyde**	**2nd Aldehyde**	**Product**	**Conversion (Isolated yield) [%]**
1				50
2				68
3				48 (36)
4				33
5				44

Simple aliphatic aldehydes were chosen to couple with 4-cyanobenzaldehyde (*Table 3.5*). Surprisingly, *iso*-butyraldehyde showed a very good conversion of 60% (*Table 3.5*, Entry 1). This is particularly remarkable, since the coupling reaction outcompetes a base-catalyzed aldol self-condensation which might have taken place due to the presence of an acidic α-proton.

For the other aliphatic aldehydes the conversions are significantly lower (between 10-27%). This is still remarkable considering the bulkiness of some aldehydes (e.g. trimethylacetaldehyde) and the functional groups that are present. In particular, entries 3 and 4 in *Table 3.5* show that functional groups such as amino are no inherent limitation to the reaction.

The final coupling substrate was *trans*-cinnamaldehyde. In this case a moderate conversion of 37% was achieved (*Table 3.5*, Entry 5). Nevertheless, it demonstrates that even the reactivity associated with the α,β-unsaturation of vinylic systems are no hindrance for the described coupling method.

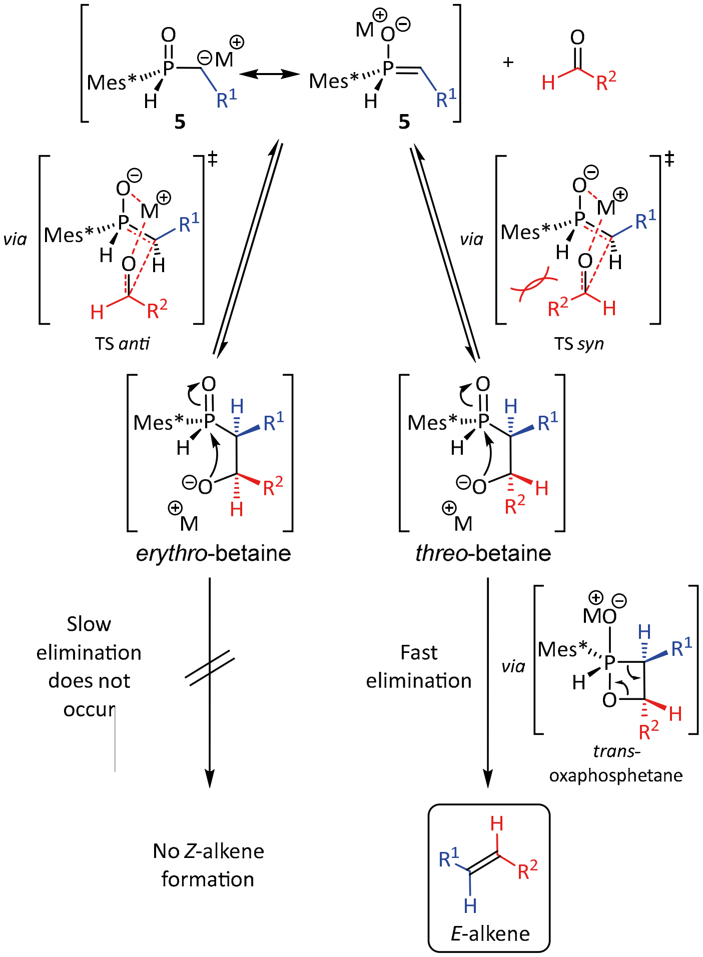
Table 3.5 Unsymmetrical *E*-alkenes from cross-couplings of 4-cyanobenzaldehyde with aliphatic and vinylic aldehydes.

Entry	1st Aldehyde	2nd Aldehyde	Product	Conversion [%]
1				60
2				27
3				24
4				10
5				37

From all the discussed examples it is clear that the substrate scope for the second step of the reaction is much larger than that of the first. This was very evident when the coupling between 4-bromobenzaldehyde and unsubstituted benzaldehyde, which resulted in 56% conversion (*Table 3.3*, Entry 2), was performed in reverse order; employing benzaldehyde in the first step followed by 4-bromobenzaldehyde in the second gave the desired product only in a very low yield.

3.7 Mechanistic aspects on stereochemical outcome

The discussion of the mechanism for the reaction of the secondary phosphine oxide **5** with the second aldehyde from a stereochemical point of view is in accordance with the mechanism of the HW reaction (compare *Scheme 2.10* in section 2.1.3). Most remarkable in our methodology is the fact that only *E*-alkenes are formed, and no traces of *Z*-alkenes were ever observed in any of the performed reactions. This is in agreement with a one-step HW and HWE reaction for the synthesis of 1,2-disubstituted alkenes.[26a, 55] One of the main reasons for the *E*-stereoselectivity is the ability of the R^1 group to provide conjugation or stabilization of the negative charge, and thus to lower the activation energy for the HW elimination. Another factor is the reversibility of the aldehyde addition to a phosphine oxide bearing an anion-stabilizing group. The reversibility of the HW addition allows interconversion of the two diastereomers, and a faster elimination from the *syn*-adduct leads to selective formation of the *E*-isomer. A schematic representation of the mechanism with corresponding “betaine-type”[55] intermediates is depicted in *Scheme 3.15*.


5
5
via
TS anti
via
TS syn
erythro-betaine
threo-betaine
Slow elimination does not occur
No Z-alkene formation
Fast elimination
via
trans-oxaphosphetane
E-alkene

M = Li, tetrabutylammonium

R^1 = electron-deficient phenyl or heterocycle with anion-stabilizing group

R^2 = aryl, heteroaryl, aliphatic, vinylic (electron-deficient)

Scheme 3.15 Proposed mechanism for the selective formation of *E*-alkenes from the reductive aldehyde cross-coupling of two aldehydes in accordance to HW reaction.[55]

In principle, the formation of the *erythro* intermediate is preferred since during an *anti*-addition of the aldehyde the steric clash between the phosphine oxide group with Mes* and the aldehyde is smaller. However, due to a slow elimination from the *erythro* intermediate and an increased rate of the HW reverse reaction no *Z*-alkene is formed. In fact, the slow elimination from the *erythro* intermediate is in competition with the equilibrium for the HW addition and the fast elimination from the *threo* intermediate. The irreversible elimination from the *threo* intermediate leads to the formation of the thermodynamically favored *E*-alkene, and hence consumes all starting material. This is also in agreement with the HWE reaction where the rate for the last elimination step is faster for the *trans*-oxaphosphetane.[10a, 14b] Furthermore, WARREN *et al.* showed that equilibration can also occur during the elimination step from an isolated and stereochemically pure *β*-hydroxy phosphine oxide which can result in "stereochemical leakage".[56, 137]

3.8 Advantages and limitations

In comparison to the MCMURRY reaction, the method described in this chapter has some notable advantageous features which we outline here.

Our reaction uses a phosphanylphosphonate reagent that is prepared on a multi-gram scale without the necessity of a transition metal during any step of the coupling reaction. In the case of the MCMURRY reaction, low-valent Ti reagents need to be prepared *in situ* from $TiCl_3$ or $TiCl_4$ in combination with a reducing agent such as Zn or Zn-Cu which makes it particularly difficult to achieve reproducible yields.[10a] All transformations in our couplings are carried out under mild conditions at room temperature and within a few minutes, whereas the MCMURRY coupling typically requires refluxing in high-boiling solvents for extended periods of time. Due to strong reducing conditions some functional groups are not tolerated in the MCMURRY reaction which is not a problem in our coupling. From a stereochemical point of view, our novel methodology selectively generates only *E*-alkenes; in all cases with no traces of the *Z*-isomer. In the MCMURRY coupling the thermodynamically favored *E*-isomer is predominant, but often *E*/*Z*-isomeric mixtures are formed.[116a] Most importantly, our coupling reaction benefits from an ionic mechanism that allows a selective cross-coupling of two *different* aldehydes to form unsymmetrical 1,2-disubstituted *E*-alkenes in a controlled manner. This constitutes a vast improvement compared to the MCMURRY protocol, where due to the radical mechanism at best statistical mixtures of the two homo-coupled products and the desired dissimilarly substituted olefinic product are obtained.[122] In such a case, tedious purification steps are required to isolate the unsymmetrical product from the statistical mixture. These steps are completely avoided in our protocol, and thus higher yields for the unsymmetrically substituted product can be achieved.

Compared to WITTIG or HWE-type chemistry our procedure is a one-pot reaction which means that it omits the necessity to synthesize bromide and ylide or phosphonate precursors. A typical 2-3 steps sequence for the preparation of these reagents is avoided and feedstock aldehydes can be used directly. This advantage applies also in comparison with the JULIA and PETERSON olefinations which are based on olefinating reagents. Moreover, in the JULIA-LYTHGOE reaction two steps and a trapping of the intermediate species are necessary. This is avoided in our one-pot protocol. The use of reductant in the last step of the Julia-Lythgoe olefination lowers the functional group tolerance. Comparing with the PETERSON reaction our method has some benefits from a stereochemical point of view. The reaction of α-silyl carbanions with electron withdrawing groups generates diastereomeric mixtures of the intermediate *β*-hydroxysilanes that immediately decomposes to *E*/*Z* product mixtures. In our case only *E*-alkenes are obtained.

However, like many reactions in organic chemistry, also our methodology has some intrinsic limitations. The limitations arise from the reaction's substrate scope. First, only couplings between two aldehydes are possible and second, the aldehydes need to be electron-poor (activated). Although, the scope for the second aldehyde is broader (neutral aromatic, vinylic and aliphatic), it is crucial that the first aldehyde is electron-deficient with EWG. If the first aldehyde has very electron-donating substituents, the polarity of the double bond in the intermediate phosphaalkene might resemble an inversely polarized phosphaalkene. This is disadvantageous for the coupling step since it can greatly decrease the reactivity. Substituents, such as amino-groups with strong electron donating properties, lower the electrophilicity of the phosphorus atom. In a more extreme case, they lead to an inverse reactivity behavior in which the nucleophile attacks on the carbon instead on the phosphorus center (see *Scheme 3.5*).[58b, 99b, 103] Knowing these limitations is key to rational improvements of the coupling method. A more detailed discussion focusing on a strategy on how to improve the substrate scope is given in the beginning of chapter 4.

3.9 Conclusions

The present one-pot reaction provides a first example of a transition metal-free *direct* reductive aldehyde-aldehyde coupling to form 1,2-disubstituted *E*-alkenes with excellent stereoselectivity. It shows vast improvement on the MCMURRY coupling, and is based on a phosphorus coupling reagent, namely phosphanylphosphonate **1**. This functions as both a reducing agent and oxygen acceptor. The selectivity for the formation of dissimilarly 1,2-disubstituted *E*-alkenes stems from the fact that the one-pot procedure is a series of three elementary reaction steps (see illustration in *Figure 3.5*): conversion of the first aldehyde to a phosphaalkene intermediate, activation of the phosphaalkene by a hydroxide base, and olefination of the second aldehyde with the *in situ* generated intermediate phosphine oxide. Due to the ionic mechanism, mild conditions and short reaction times, this methodology allows the coupling of electron deficient aldehydes in good overall yields.

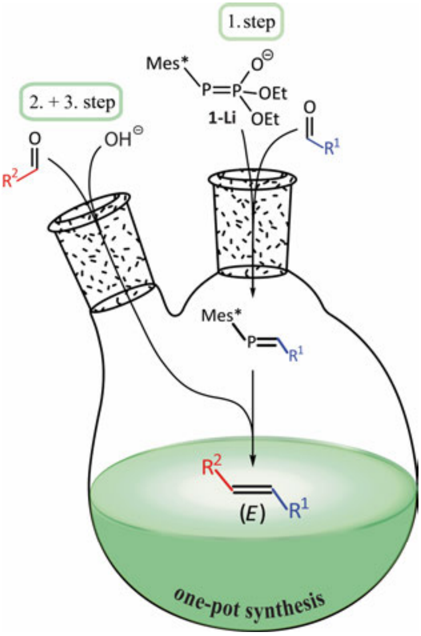

1. step
Mes*
P=P
O⊖
OEt
OEt
1-Li
O
R1
2. + 3. step
O
R2
OH⊖
Mes*
P=
R1
R2
(E)
R1
one-pot synthesis

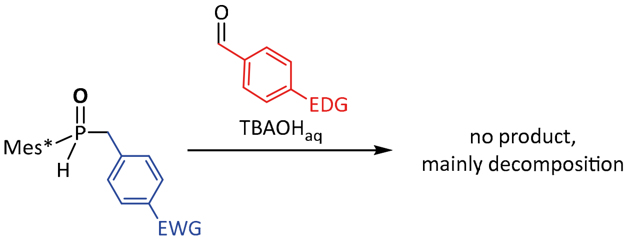
Figure 3.5 Summarizing illustration of the stereoselective synthesis of unsymmetrical *E*-alkenes from *two* different aldehydes in a one-pot protocol.

4. Method optimization and modification for broadening the substrate scope (Paper II)

This chapter describes a modification to the method discussed in the previous chapter which is based on the substitution of a hydrogen atom on the phosphorus center of the phosphine oxide intermediate by an alkoxide group. The strategies for enhancing reactivity, the optimization of reaction conditions and increasing substrate scope for the second coupling partner are presented herein.

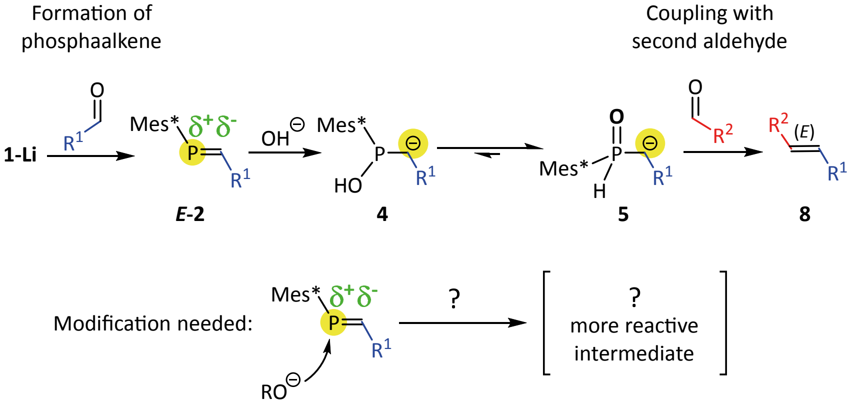
4.1 From HORNER-WITTIG to HORNER-WADSWORTH-EMMONS – strategies to overcome limitations

As described in section 3.8, only a few types of aldehydes can undergo successful coupling. For example, aromatic aldehydes with electron donating groups (EDG) are not suitable substrates in the second step of the reaction and, under the present conditions, result in decomposition and no product formation (*Scheme 4.1*).



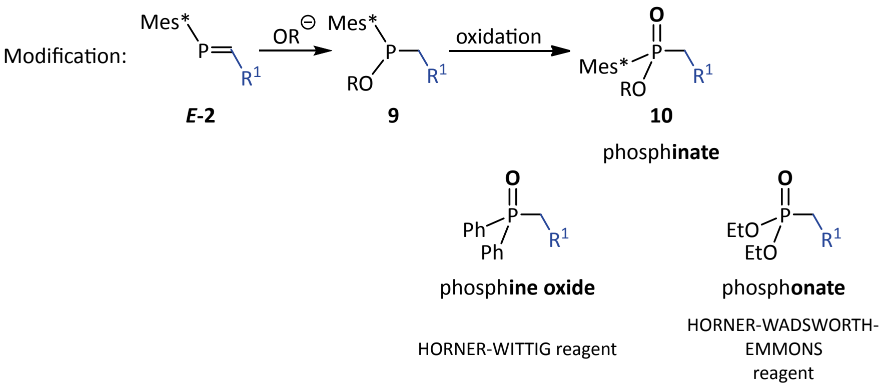
Scheme 4.1 Limitation in substrate scope: couplings with electron rich benzaldehydes as second aldehyde are not possible.

In order to find ways to broaden the substrate scope, a closer look into the chemistry of the phosphaalkene and phosphine oxide key intermediates is essential. In the first step of the coupling sequence the carbonyl carbon undergoes an inversion of polarity (Umpolung) from δ^+ to δ^-. Consequently, this effect leaves a partial positive charge on the phosphorus and an electrophilic P=C bond. During the nucleophilic attack by hydroxide the P=C bond gets activated which enhances the nucleophilicity of the C-center. These are the two factors that define the limitations: the electrophilicity of the P-center in the phosphaalkene and the nucleophilicity of the C-center in the phosphine oxide (marked with yellow circles in *Scheme 4.2*). Hence, a more reactive intermediate phosphaalkene or phosphine oxide is needed (*Scheme 4.2*, bottom).



Scheme 4.2 Representation of two main factors for the reaction's outcome: reactivity of P=C bond towards nucleophiles and nucleophilicity of the SPO carbanion (top). Modification of the phosphaalkene intermediate is needed (bottom).

In principle, there are two main strategies to overcome the limitations in the reaction scope. Both refer to the intermediate phosphaalkene species. One strategy is to reduce the steric bulk or kinetic protection of the substituent on the phosphorus atom. A second strategy concerns the electronic properties of the phosphaalkene and in particular the P=C bond. It is important to enhance its polarity and thus, to increase the electrophilicity of the P-center for a more facile nucleophilic attack. But even more important is to increase the reactivity of the phosphine oxide by increasing its nucleophilicity of the C-center. This chapter deals with the latter. We hypothesized that the presence of more oxygen substituents at the P-center should increase the acidity of the α-protons which would result in a more nucleophilic C-center. Indeed, such a deliberation has led to the development of the classical HORNER-WADSWORTH-EMMONS reagents derived from HORNER-WITTIG reagents almost sixty years ago.[13-14] From a synthetic point of view we targeted a sequence in which phosphaalkene ***E*-2** is first converted to a phosphinite **9**, followed by oxidation to a phosphinate **10** prior to the coupling with the second aldehyde (*Scheme 4.3*).



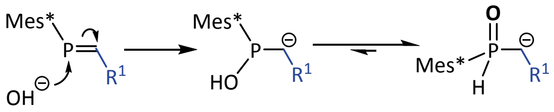
Scheme 4.3 Modified reaction sequence with addition of alkoxide to a phosphaalkene and subsequent oxidation to yield a phosphinate intermediate (R = Et or Me). In comparison phosphine oxide (HW) and phosphonate (HWE) reagents are shown.

4.2 Substituent effects in phosphaalkenes

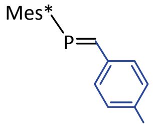
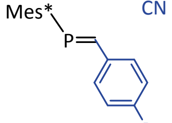
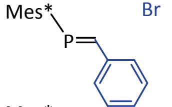
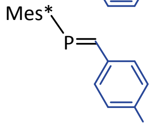
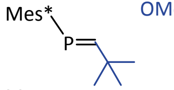
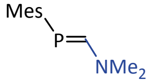
As mentioned in section 4.1, the electrophilicity of the P-center in the phosphaalkene and the nucleophilicity of the C-center of the phosphine oxide mainly control the reactivity for the coupling with the second aldehyde. Both are strongly influenced by the type of the first aldehyde and explicitly by its *para*-substituent. Phosphaalkenes with electron-withdrawing C-substituents such as 4-cyanophenyl, 4-bromophenyl, and pyridyl increase the electrophilic character of the P=C bond and engage in facile hydrolysis by $TBAOH_{aq}$ within a few minutes. Conversely, unsubstituted phenyl phosphaalkenes like Mes*P=C(*Ph*)H are less reactive and are only hydrolyzed after 45 min. Even less reactive are phosphaalkenes with electron-donating substituents or with aliphatic groups (e.g. Mes*P=C(*t-Bu*)H) which are completely unreactive towards hydroxide attack after prolonged reaction times. Although it should be mentioned at this point that in case of Mes*P=C(*t-Bu*)H also steric bulk needs to be considered as a reason for the inertness against hydrolysis. Even if the corresponding phosphine oxides are formed, the EDGs lower the acidity of the α-proton and lead to a stalled reaction sequence. This makes EDG containing aldehydes generally unsuitable as the first substrate.

Interestingly, the reactivity of phosphaalkenes towards nucleophilic attack by hydroxide correlates with its ^{31}P NMR chemical shift values δ_{31P} (see *Table 4.1*). This observation is also in agreement with the linear correlation between the values of δ_{31P} and Hammett-type substituent constants σ, and reveals that δ_{31P} is rather sensitive to substituents at the double bond.[58a, 59, 82d, 83d, 129a, 138] Phosphaalkenes with a more deshielded P-atom (downfield chemical shifts) are better electrophiles and react extremely fast. This is exemplified by phosphaalkenes ***E*-2** with 4-cyanophenyl, 4-bromophenyl and 4-methoxyphenyl substituents with ^{31}P NMR shifts of 284, 264, and 246 ppm, respectively. Consequently, only phosphaalkenes with chemical shifts higher than 260 ppm are suitable substrates for the first step of the coupling sequence.

Table 4.1 Reactivity behavior of phosphaalkenes against hydroxide attack in correlation with ^{31}P NMR chemical shift values (δ_{31P}).



more deshielded P-center

Phosphaalkene	Chemical shift value δ_{31P} [ppm][83d]	Hydrolysis of P=C
	284	Immediate
	264	Immediate
	259	45 min
	246	No reaction
	241	No reaction
	60[82b, 103]	Inverse reactivity[58b]

In a more extreme case, if the first aldehyde is very electron-rich (e.g. MesP=C(*NMe₂*)H, last entry in *Table 4.1*) with strong electron donating substituents, the intermediate phosphaalkenes has inversely polarized character. This features also in ^{31}P NMR spectroscopy since such molecules show chemical shifts at unusually high fields, whereas in normally polarized phosphaalkenes low-field ^{31}P NMR resonances are typical (compare in *Table 4.1*).[58b, 87, 103, 139] From a reactivity point of view, such aldehydes are in principle not suitable for the reductive cross-coupling.

The substituent effect is also important for the stabilization of the anionic intermediate phosphine oxide **5** and phosphinate **10**. Since it affects the level of nucleophilicity, best results are obtained with more stabilized carbanions. This trend in reactivity is comparable to corresponding HWE-type olefinations. The best conversions are obtained with the 4-cyanobenzyl substituent where the negative charge on the C-atom is highly stabilized by resonance with the cyano moiety (*Figure 4.1*).

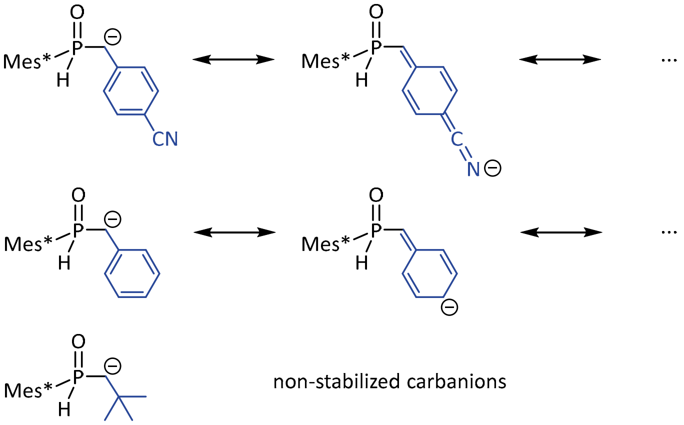
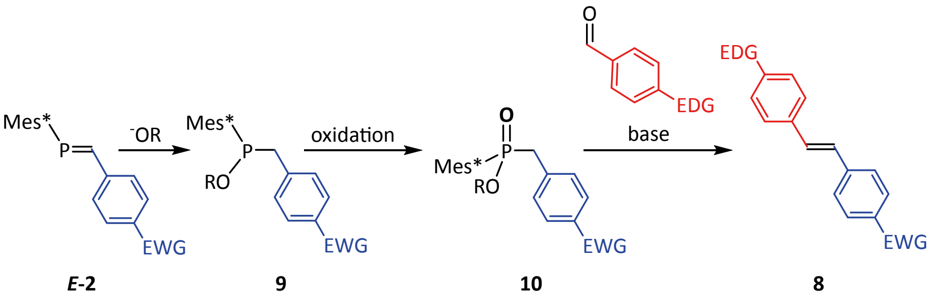


Figure 4.1 Resonance stabilization effect in phosphine oxide anions bearing different substituents.

A certain amount of resonance is even possible with a simple phenyl ring without the cyano substituent, although it is less effective. For the case of aliphatic groups (e.g. *t*-butyl) such stabilization is completely absent and also explains the lack of reactivity for such type of phosphine oxides.

4.3 Reactivity enhancement *via* increased amount of oxygen substituents on intermediate phosphorus species

Following the hypothesis of an increased reactivity for a phosphinate *versus* phosphine oxide intermediate (see section 4.1), the coupling sequence was modified with the aim to enlarge the scope for the second aldehyde. Instead of addition of $TBAOH_{aq}$ to the phosphaalkene intermediate ***E*-2** like in the initial protocol (see chapter 3), an alkoxide is added and the transient phosphinite **9** is oxidized to the corresponding phosphinate **10**. The phosphinate **10** is expected to be more reactive than a phosphine oxide in the final coupling step (*Scheme 4.4*).


Mes*
P
⁻OR
Mes*
P
RO
oxidation
O
P
Mes*
RO
O
EDG
base
EDG
EWG
EWG
EWG
EWG
E-2
9
10
8

Scheme 4.4 Modified coupling sequence *via* phosphinate intermediate.

Initial support for our hypothesis was obtained from DFT calculations at the B3LYP level of theory with a 6-311G(d,p) basis set, which showed a higher Mulliken charge at the P-center in phosphinate **10** (+1.246) in comparison to that in phosphine oxide **5** (+0.986). The corresponding optimized molecular structures with calculated Mulliken charges are shown below in *Figure 4.2*.

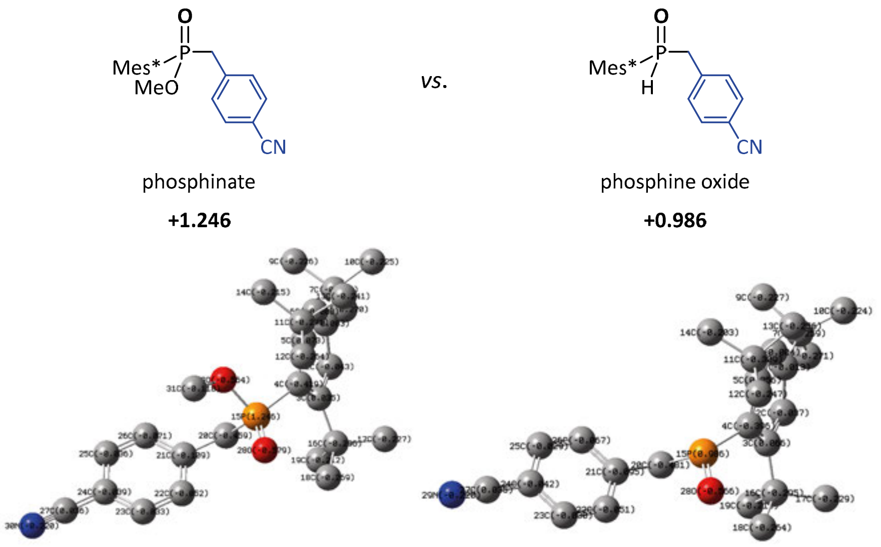

O
P
Mes*
MeO
CN
phosphinate
+1.246
vs.
O
P
Mes*
H
CN
phosphine oxide
+0.986

Figure 4.2 Molecular structures for phosphinate **10** and phosphine oxide **5** (with 4-cyanobenzyl substituent and R = Me) after geometry optimization. Hydrogen atoms omitted for clarity. Corresponding Mulliken charges are indicated.

4.3.1 Nucleophilic addition of alkoxides to intermediate phosphaalkenes

The reactivity of the phosphaalkene intermediate with a range of alkoxide salts was tested. The test reactions were performed on isolated phosphaalkenes Mes*P=C($4\text{-}CNC_6H_4$)H and Mes*P=C($4\text{-}BrC_6H_4$)H. The results are summarized in *Table 4.2*. It was found that ethanol is not nucleophilic enough to add to the P=C bond. Furthermore, solid sodium methoxide (NaOMe) and potassium *tert*-butoxide (*t*-BuOK) do not react with the phosphaalkene either, presumably due to their low solubility in THF. A 1 M lithium ethoxide (LiOEt) solution in THF also showed no reactivity. For a successful addition of an alkoxide to the phosphaalkene a combination of an alkoxide source and the corresponding alcohol is necessary. For example, some reactivity was observed in case of sodium ethoxide and methoxide solutions in ethanol and methanol, respectively. Further increased reactivity was obtained with a solution of tetrabutylammonium ethoxide (TBAOEt) in ethanol and a methanolic tetrabutylammonium methoxide (TBAOMe) solution. Both led to full conversion of the phosphaalkenes ***E*-2** to the corresponding phosphinites **9** within a few minutes.

Table 4.2 Different alkoxide sources and their ability for the nucleophilic addition to phosphaalkenes.

Alkoxide reagent	**Nucleophilic attack on phosphaalkene**
EtOH	No reaction
NaOMe (powder)	No reaction
t-BuOK (powder)	No reaction
LiOEt (1 M solution in THF)	No reaction
NaOEt (21 wt. % solution in EtOH)	Several hours
NaOMe (25 wt. % solution in MeOH)	Several hours
TBAOEt (40 wt. % solution in EtOH)	Few minutes
TBAOMe (20 wt. % solution in MeOH)	Few minutes

As described in section 4.2, the rate of the nucleophilic addition to the P=C bond is strongly dependent on the electronic nature of the C-substituent. Hence, a reactivity behavior analogous to that in *Table 4.1* for hydroxide attack at phosphaalkenes, was also observed in case of a TBAOMe/MeOH solution. In a comparative study, the addition of methanol to phosphaalkenes with different *para*-substituents X on their aromatic ring was followed by ^{31}P NMR spectroscopy. As shown in *Figure 4.3*, electron-poor phosphaalkenes (X = CN, Br) are consumed quickly and the phosphinites are formed within a few minutes after TBAOMe addition. Unsubstituted phenyl phosphaalkenes (X = H) react within one hour, while electron-rich phosphaalkenes do not show a reactivity even after prolonged reaction times. This reactivity trend is the reason for using electron-deficient aldehydes in the first step of the cross-coupling reaction. Hence, only 4-cyano- and 4-bromobenzaldehyde will be considered as substrates.

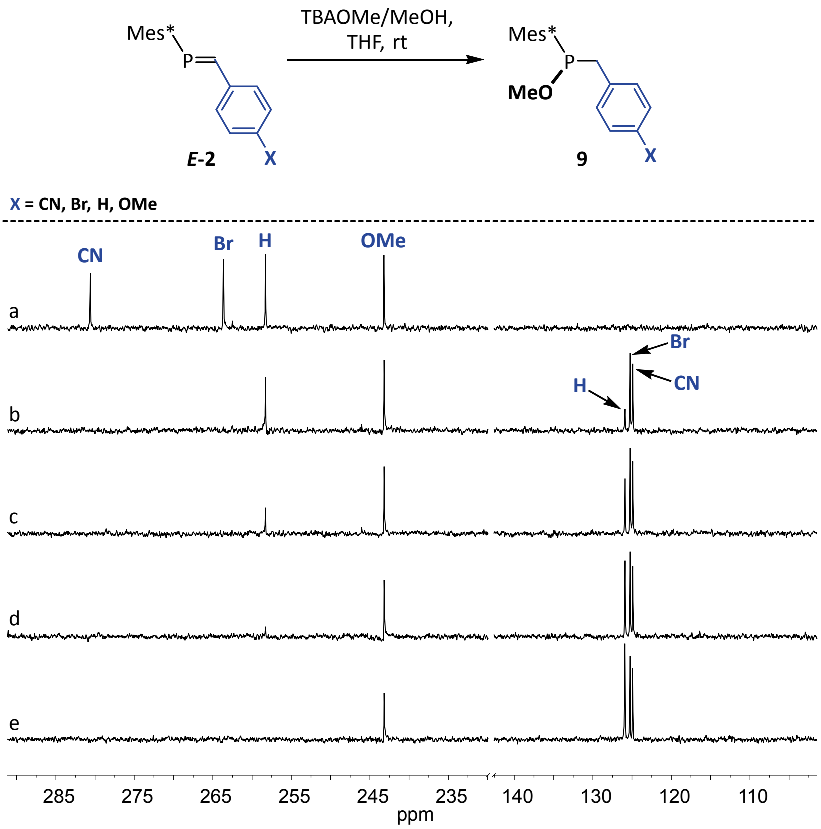


Figure 4.3 ^{31}P NMR spectroscopic monitoring of the addition of a methanolic tetrabutylammonium methoxide (TBAOMe/MeOH) solution to a mixture of phosphaalkenes with electron-withdrawing (X = CN, Br), neutral (H) and electron-donating (OMe) substituents. a) Mixture of phosphaalkene starting materials. After different reaction times with TBAOMe/MeOH: b) 7 minutes, c) 22 minutes, d) 53 minutes, e) 2.5 hours.

4.3.2 Oxidation of intermediate phosphinites to phosphinates

A variety of oxidants can be used for the conversion of phosphinites **9** to their corresponding phosphinates **10**.[100] *Table 4.3* summarizes the results of tested oxidants.

Table 4.3 List of oxidants tested for the oxidation of phosphinite **9** to phosphinate **10**.

Oxidant	Result
Air	No reaction
Trimethyl-N-oxide	No reaction
H_2O_2 urea complex	Very slow (very low solubility)
H_2O_2 (35% aq. solution)	10 minutes at room temperature
t-BuOOH (water-free benzene solution)	4-5 hours at room temperature

For our reaction sequence water-free *t*-BuOOH in benzene gives the most satisfactory results. An aqueous hydrogen peroxide solution can be used as well, and leads to a fast conversion. However, it was found that side reactions with substituents such as cyanides may occur. Due to the presence of water and the oxidative environment the cyano-group can hydrolyze to an amide.[140] Under these conditions, a crystal structure of phosphinate **10** could be obtained (*Figure 4.4*). Compound **10** crystalizes in the same triclinic P -1 space group as phosphine oxide **5-H**. In comparison to the crystal structure of **5-H** (with substituent X = CN), the bond length between phosphorus and the α-carbon atom is 0.025 Å shorter (P1-C2 = 1.810(5) Å; in **5-H**: 1.835(2)). This bond shortening is in agreement with a more polar P-C bond which is the result of the additional alkoxy substituent at the P-center in **10**.

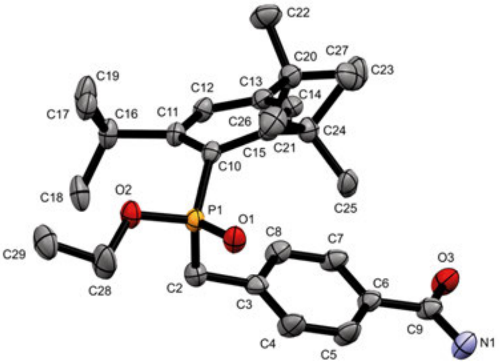


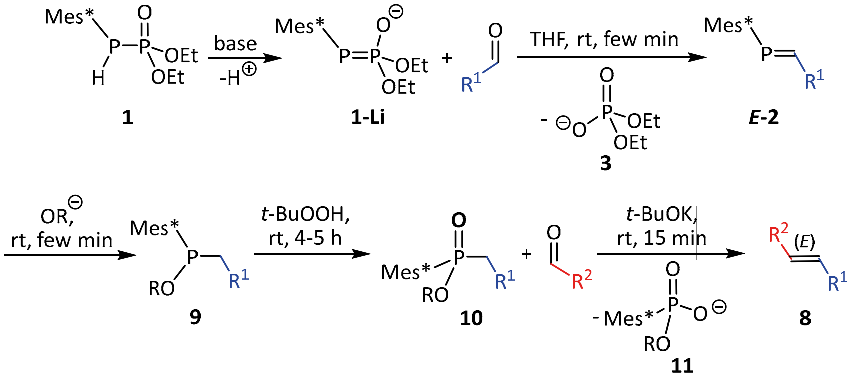
Figure 4.4 ORTEP plot of phosphinate **10** (with R = Et and R^1 = 4-carbamoylbenzyl) at 50% probability ellipsoids. All hydrogen atoms are omitted for clarity. Selected bond lengths: P1-C10 1.826(4) Å, P1-O1 1.478(3) Å, and P1-O2 1.579(4) Å.

As mentioned above, the oxidation with an aqueous H_2O_2 solution simultaneously hydrolyzes the cyanide. This can be observed by ^{31}P NMR spectroscopy since the newly formed amide substituent leads to a slightly deshielding effect on the P-atom and thus, a minor change of the ^{31}P chemical shift values for the corresponding phosphinates (δ_{31P} = 41.4 ppm for **10** with X = CN and 42.5 ppm for **10** with X = $CONH_2$).

4.3.3 Modified coupling sequence applied to one-pot protocol

With optimized reaction conditions for the alkoxide addition and oxidation in hands, we incorporated them into a modified one-pot protocol for the full cross-coupling of two *different* aldehydes. The complete reaction with the corresponding modifications is shown in *Scheme 4.5*.

After formation of phosphaalkenes, either an ethanolic solution of tetrabutylammonium ethoxide (TBAOEt) or the corresponding methanolic TBAOMe solution is added at room temperature. This results in fast nucleophilic attack of the alkoxide at the P-center and formation of the transient phosphinite species **9** which is oxidized in the next step within 4-5 hours by an anhydrous benzene solution of *t*-BuOOH. For the final coupling step an additional base is needed. $\mathrm{TBAOH_{aq}}$ was tested on the isolated phosphinate intermediate **10**, but the reaction was slow and sluggish leading to decomposition and side products. Potassium *tert*-butoxide (*t*-BuOK), which is a standard base in HW- and HWE-type olefinations,[10a, 55] showed best results and product formation was observed within 15 minutes at room temperature.



Scheme 4.5 One-pot reaction for the reductive cross-coupling of two different aldehydes to unsymmetrical *E*-alkenes *via* phosphinate intermediate **10** (R = Et or Me).

Similarly to the protocol discussed in chapter 3, each step of the cross-coupling reaction can conveniently be monitored by ^{31}P NMR spectroscopy. *Figure 4.5* shows the ^{31}P NMR spectra for each step of the coupling reaction between 4-cyano- and 4-methoxybenzaldehyde. A smooth formation of phosphaalkene ***E*-2** from first aldehyde and **1-Li** (*via* deprotonation of **1**) (a → b →c) is followed by the addition of TBAOMe/MeOH which converts ***E*-2** to phosphinite **9** (^{31}P NMR resonance at about 125 ppm) and the phosphate by-product **3** (c → d). As expected, oxidation to phosphinate **10** leads to an additional upfield shift to 45 ppm (d → e). Although the reaction conditions are basic, the acid/base equilibrium for **10** is lying on the side of the protonated form. Therefore, additional *t*-BuOK is needed in order to drive the final step of the reaction to full conversion. The reaction of **10** with the second aldehyde gives the desired alkene and the phosphonate by-product **11** in short times of about 15 minutes (e → f).

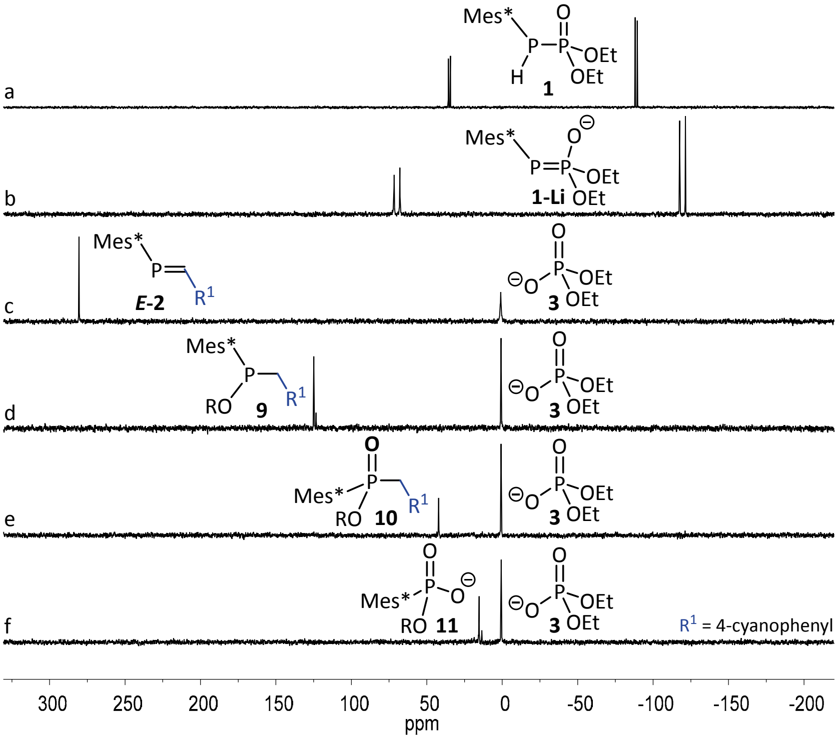
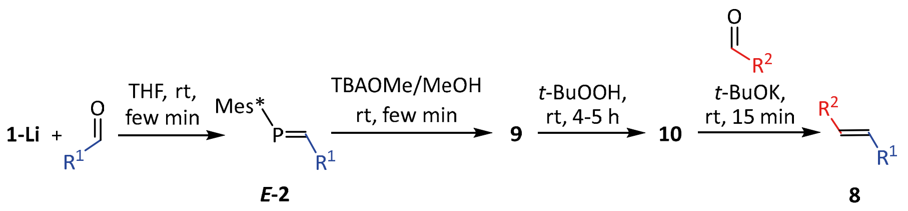


Figure 4.5 ^{31}P NMR monitoring of individual reaction steps. (a → b) Deprotonation of phosphanylphosphonate **1** to **1-Li**. (b → c) Formation of phosphaalkene ***E*-2** and the diethyl phosphate by-product **3**. (c → d) Further conversion to phosphinite **9** and (d → e) oxidation to phosphonate **10**. (e → f) Final step in the reaction of **10** with a second aldehyde to yield the alkene product and the Mes*-phosphonate by-product **11** (R^1 = 4-cyanophenyl).

4.4 Substrate scope

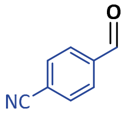
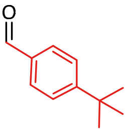
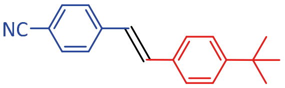
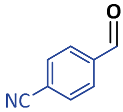
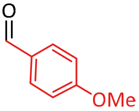
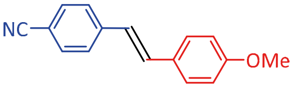
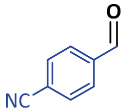
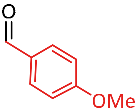
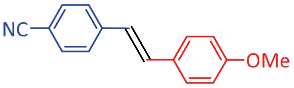
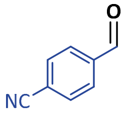
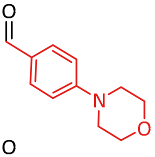
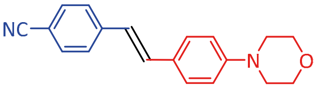
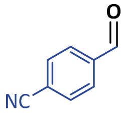
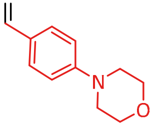
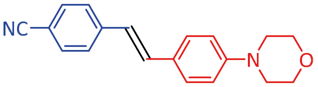
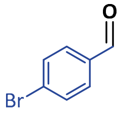
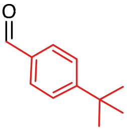
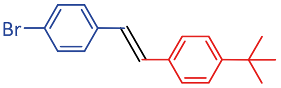
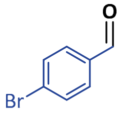
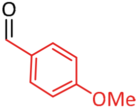
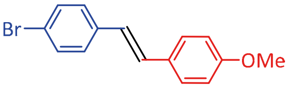
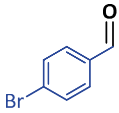
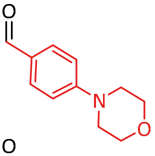
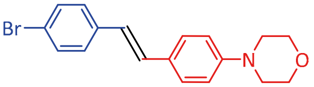
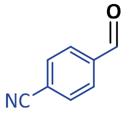
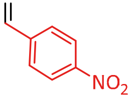
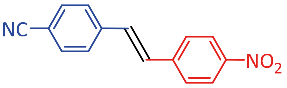
4.4.1 Unsymmetrical *E*-alkenes with push-pull electronic properties



With the modified procedure in place, the reactivity towards deactivated, electron-rich aldehydes as substrates for the second step was explored. Much to our satisfaction, benzaldehydes with electron-donating substituents such as 4-methoxy- or 4-morpholinobenzaldehydes react well and the unsymmetrical stilbenes with push-pull electronic properties are formed without any traces of the symmetric product (*Table 4.4*). Such types of stilbenes are important building blocks in organic electronics and photonic materials.[7a, 141]

Like in the previous protocol (chapter 3), the reaction is highly selective for the *E*-stereoisomer. The overall yields are decent to good and similar to olefinations of unreactive aldehydes that use classical HWE reagents.[14b] However, the advantage of our methodology is that the preparation of the HWE phosphonate reagents is avoided and two aldehydes can be used directly. Furthermore, if the second aldehyde is economically valuable, it can be used as the limiting reagent. Addition of 0.5 equivalents (relative to phosphanylphosphonate **1**) of second aldehyde leads to distinct increase of the overall yields of the coupling to 70-80% isolated yields (see Entries 2' and 3' in *Table 4.4*). Noteworthy is the coupling between 4-cyano- and 4-nitrobenzaldehyde in 67% yield (Entry 7, *Table 4.4*). This is remarkable in comparison to the McMURRY coupling as neither of these functional groups are compatible with the radical mechanism and the highly reducing reaction conditions.[20a, 142]

Table 4.4 Unsymmetrical *E*-stilbenes from two different aldehydes with electron withdrawing (1st aldehyde) and electron-donating (2nd aldehyde) *para*-substituents (except entry 7). [a]Coupling was performed with 0.5 equivalent of the 2nd aldehyde.

Entry	1st Aldehyde	2nd Aldehyde	Product	Isolated yield (Conversion) [%]
1				53 (59)
2				51 (56)
2’				79[a]
3				39 (45)
3’				70[a]
4				50 (57)
5				44 (51)
6				35 (39)
7				67

4.5 Conclusions

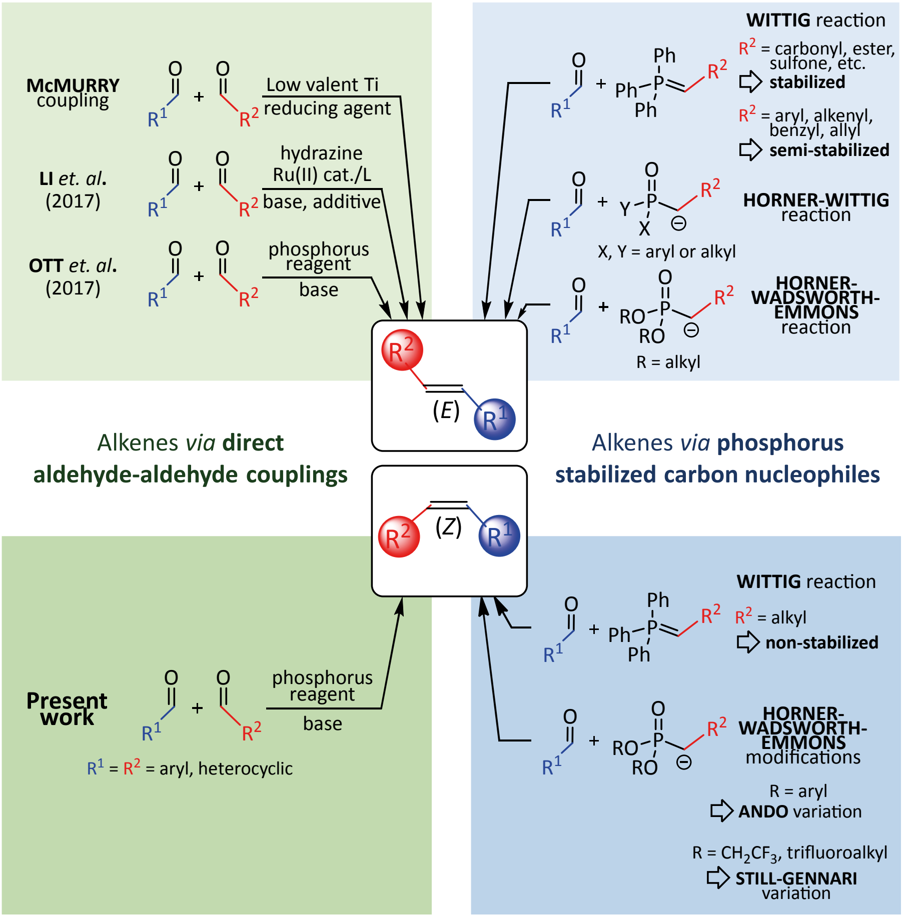
In summary, we could extend the protocol for the one-pot reductive cross-coupling and enlarge the substrate scope for the use of deactivated aldehydes in the final coupling step. The modification of the original procedure is based on an increased amount of oxygen substituents at the P-center which displays an enhanced reactivity for the phosphinate intermediate **10** towards electron-rich benzaldehydes. This allows a facile formation of *trans*-stilbenes with push-pull electronic properties directly from two *different* aldehydes.

5. Selective formation of *Z*-alkenes by a novel *phospha*-HWE coupling reagent (Paper III)

This chapter describes the development of a new *phospha*-HWE reagent for the one-pot reductive coupling of aldehydes with high *Z*-selectivity. The synthesis route for the reagent, its application to aldehyde couplings in a one-pot procedure, stereochemical investigations and mechanistic discussion are presented.

5.1 Stereoselective access to *Z*-alkenes – literature methods

Typical methods for the preparation of alkenes have been presented in detail in previous chapters. *Scheme 5.1* exhibits a graphical overview for methodologies to access either *E*- or *Z*-alkenes *via* aldehyde-aldehyde couplings (*left side*) or reactions between one aldehyde and an organophosphorus olefinating reagent (*right side*). The majority of the existing synthetic methods yield preferentially *E*-alkenes. The main methods for the direct coupling of two aldehydes are the MCMURRY coupling, LI *et al.*'s method, and our new methodology presented in chapter 3 and 4 of this thesis (*top left*). *E*-alkenes are also the major products of WITTIG-type reactions with phosphorus stabilized carbon nucleophiles (*top right*). Much fewer procedures exist for the selective formation of *Z*-alkenes (*bottom right*).[30, 143] *Z*-alkenes can be obtained from WITTIG reactions only with non-stabilized phosphonium ylides.[26c] In this regard, the HWE reaction is more widely used due to its versatility, amenability and tuneability of the stereochemical outcome by introducing different types of substituents $-(OR)_2$ or $-(NR_2)_2$ at the P atom.[10a] It has been shown that bulky and electron withdrawing moieties R lead to a higher proportion of the *Z*-isomer.[143] Thus, extensive efforts have been devoted to modifications of the HWE reaction in order to achieve the stereoselective formation of *Z*-olefins. Numerous variations have been reported, e.g. by COREY and KWIATKOWSKI[144] (1966), BREUER[145] (1977), STILL and GENNARI[146] (1983), PATOIS and SAVIGNAC[147] (1991), ANDO[148] (1995), EVANS[149] (1996) and the group of AKIBA[150] (1997). The molecular structures of the corresponding phosphonate derivatives and related P^V reagents are represented in *Figure 5.1*.


McMURRY coupling
Low valent Ti
reducing agent
LI et. al. (2017)
hydrazine
Ru(II) cat./L
base, additive
OTT et. al. (2017)
phosphorus reagent
base
WITTIG reaction
R2 = carbonyl, ester, sulfone, etc.
stabilized
R2 = aryl, alkenyl, benzyl, allyl
semi-stabilized
HORNER-WITTIG reaction
X, Y = aryl or alkyl
HORNER-WADSWORTH-EMMONS reaction
R = alkyl
(E)
(Z)
Alkenes via direct aldehyde-aldehyde couplings
Alkenes via phosphorus stabilized carbon nucleophiles
Present work
phosphorus reagent
base
R1 = R2 = aryl, heterocyclic
WITTIG reaction
R2 = alkyl
non-stabilized
HORNER-WADSWORTH-EMMONS modifications
R = aryl
ANDO variation
R = CH2CF3, trifluoroalkyl
STILL-GENNARI variation

Scheme 5.1 A comparison of common methodologies for the formation of alkenes from carbonyl compounds. *Top left*: Methods that use directly two aldehydes to prepare *E*-alkenes. *Top right*: *E*-alkenes from WITTIG-type olefinations. *Bottom right*: WITTIG reaction with non-stabilized ylides and HWE modifications to access *Z*-alkenes. *Bottom left*: Novel phosphorus mediated method for the preparation of *Z*-alkenes *via* direct aldehyde-aldehyde couplings.

However, among all of them the STILL-GENNARI variant is the most established and widely recognized. It uses bis(trifluoroethyl)phosphonates to prepare *Z*-olefins.[146] Since most of the *Z*-selective olefinations require highly functionalized reagents (*Figure 5.1*) and specific reaction conditions (e.g. low temperatures, particular bases and additives, salt-free conditions)[10a, 30, 146] their general use is somewhat limited.

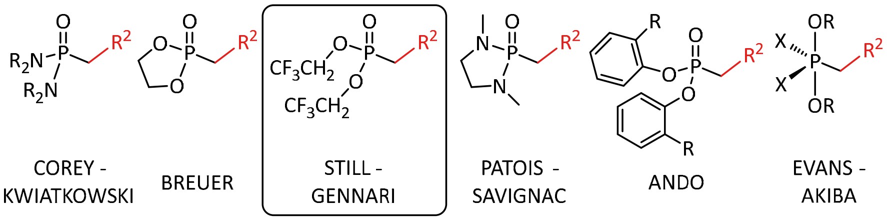


Figure 5.1 Molecular structures of modified HWE reagents for *Z*-selective olefinations.

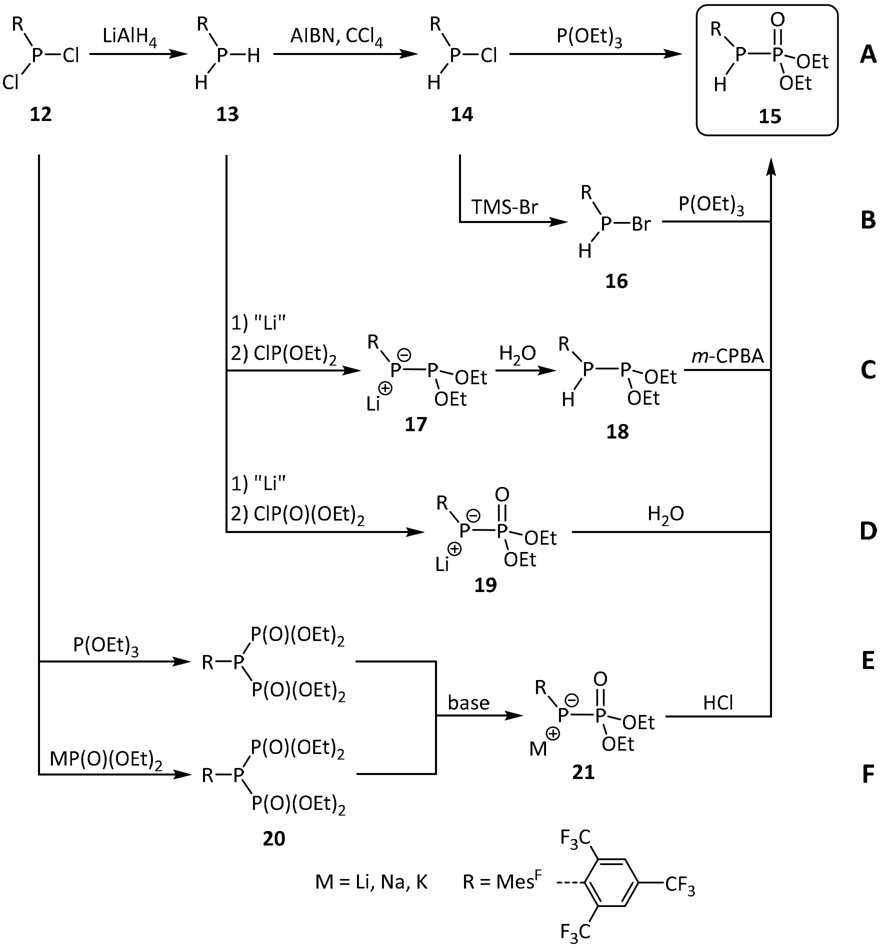
If we look back to the coupling of two aldehydes, there is no literature method describing a direct way to obtain alkenes with high *Z*-selectivity from two aldehydes (*bottom left* in *Scheme 5.1*). Inspired by the Still-Gennari modification that uses strong electron withdrawing moieties on the phosphonates, we decided to tune our previous methodology for a high *Z*-selectivity by incorporating CF_3 substituents on the protecting group of the phosphanylphosphonate reagent **1**. Sterically the CF_3 groups are very similar to the *tert*-butyl groups in the supermesityl (Mes*) protecting group,[97b] but the strongly electron withdrawing CF_3 substituents have an immense impact on the electronic properties of the phosphaalkene key intermediate. From this a dramatic change on the reactivity of the coupling step is expected. Particularly, the stereochemical outcome is expected to be strongly influenced. Analogously to the mechanism of the Still-Gennari modification, the intermediate *cis*-oxaphosphetane species should be much more likely to undergo the irreversible decay step to the olefinic product, giving rise to an increased *Z*-isomeric ratio.[148b] In the following sections, we present the preparation of a novel *phospha*-HWE reagent and its application in a one-pot procedure that enables a direct transition metal-free formation of symmetrical alkenes with high *Z*-selectivity. At present there is no such procedure that would allow for the homo-coupling of two aldehydes to *Z*-alkenes in the literature.

5.2 Preparation of a new phosphanylphosphonate as *phospha*-HWE reagent

5.2.1 Synthetic approaches

Synthetic methods for metal coordinated *phospha*-HWE reagents were first reported by the group of Mathey[95a] in the late 80s and since then, several alternative protocols including metal-free variations were developed.[95d, 97, 151]

A summary of available synthetic strategies is presented in *Scheme 5.2*. All pathways in *Scheme 5.2* start from dichloro(2,4,6-tris(trifluoromethyl)phenyl)phosphine,[152] and were tested for the preparation of the novel phosphanylphosphonate reagent **15**. Initial attempts to apply the same conditions as for the preparation of the Mes*-protected phosphanylphosphonate **1**[97b] did not yield the desired product **15** (compare *Scheme 3.11* in chapter 3 with route **A** in *Scheme 5.2*). This method involves the monochlorination of the primary phosphine **13** and a subsequent *phospha*-MICHAELIS-ARBUZOV reaction. A modification of this procedure was also performed where **14** was transformed to the monobrominated intermediate **16** prior to the reaction with $P(OEt)_3$ (route **B**). In both cases, the reactions were not complete, and increasing the equivalents of the halogenating reagents resulted in disproportionation to **12** and **13**. In the following *phospha*-MICHAELIS-ARBUZOV step, only trace amounts of **15** and some hydrolysis side products were observed by ^{31}P NMR spectroscopy.

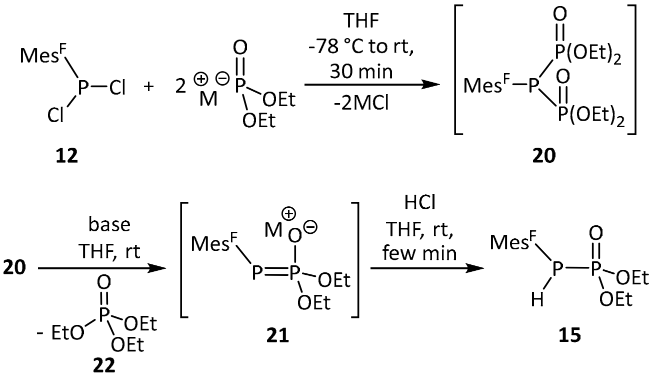

LiAlH4
AIBN, CCl4
P(OEt)3
TMS-Br
1) "Li"
2) ClP(OEt)2
H2O
m-CPBA
2) ClP(O)(OEt)2
MP(O)(OEt)2
base
HCl
12
13
14
15
16
17
18
19
20
21
A
B
C
D
E
F
M = Li, Na, K
R = MesF

Scheme 5.2 Synthetic strategies for the preparation of phosphanylphosphonate **15** with Mes^F protecting group.

Further attempts to synthesize **15** are based on the metalation of primary phosphine **13** (route **C** and **D** in *Scheme 5.2*). Herein, a primary lithiophosphine is reacted with diethyl chlorophosphite and after P-P bond formation the intermediate is oxidized by *meta*-chloroperbenzoic acid (route **C**). Alternatively, a diethyl chlorophosphate can be used in order to omit the oxidation step (route **D**). Lithiation of **13** was tested with *n*-BuLi, LDA, and MeLi in THF and Et_2O at various temperatures but conversion to **13-Li** was very low. However, neither the diethyl chlorophosphite nor the chlorophosphate showed any reactivity towards **13-Li**. The last two strategies represent a direct *phospha*-MICHAELIS-ARBUZOV (route **E**) and *phospha*-MICHAELIS-BECKER (route **F**) approach towards bis(diethylphosphoryl)phosphine intermediate **20** followed by base induced selective cleavage of one P-P bond and protonation of **21**. Formation of **20** is achieved by treating *P*,*P*-dichlorophosphine **12** either with $P(OEt)_3$ (route **E**) or with a metal salt $MP(O)(OEt)_2$ (route **F**). Both pathways yield bis(diethylphosphoryl)phosphine **20**, but using a metal salt of diethylphosphite produces a much cleaner crude reaction mixture. Therefore, route **F** was employed for the synthesis of *phospha*-HWE reagent **15**. A more in-depth analysis of this synthetic sequence is discussed in section 5.2.2.

5.2.2 Isolation and characterization

The synthetic procedure for reagent **15**, according to route **F**, is outlined in *Scheme 5.3*. In the first step, two equivalents of a diethylphosphite metal salt are used for bisphosphorylation of the starting material. The metal cation has significant influence on the success of the formation of **20**. Reaction of **12** with lithium or sodium diethylphosphite results in the generation of side products. The corresponding potassium diethylphosphite shows a very clean conversion as long as the salt is freshly prepared. In this step, it is essential to isolate the salt as a solid and not to use it as a solution prepared *in situ*, and to remove excess potassium to avoid the reduction of *P*,*P*-dichlorophosphine **12**.



Scheme 5.3 Synthetic approach towards phosphanylphosphonate **15**. Reaction is performed as one-pot synthesis without isolation of intermediates **20** and **21**.

Moreover, it is critically important that the reaction is performed at low temperatures (-78 °C) in order to ensure a quantitative conversion. For temperatures higher than 0 °C or room temperature the formation of numerous side products is observed. The intermediate bis(diethylphosphoryl)phosphine **20** features a characteristic doublet at $\delta_{31P} = 22.5$ ppm and triplet of septet at $\delta_{31P} = -58.0$ ppm in the ^{31}P NMR (C_6D_6) spectrum with coupling constants of $^1J_{P\text{-}P} = 187$ Hz and $^4J_{P\text{-}F} = 36.5$ Hz. Compound **20** was not isolated and directly used in the next step.

For a selective cleavage of one of the phosphoryl-phosphine bonds in compound **20** the choice of base is crucial. Several aspects such as steric bulk, type of counter ion, and nucleophilicity need to be considered.[97a] A range of different bases were tested including hydride, fluoride and classical oxygen bases and the results are summarized in *Table 5.1*.

Table 5.1 List of tested bases for a selective cleavage of one phosphoryl-phosphine bond in compound **20**. [a]Used as solid and dissolved in THF with 5 mol% of 18-crown-6 ether.

Type of base	Result
$NaNH_2$ (solution in THF)[a]	No reaction
NaH (solution in THF)[a]	No reaction
KF (solution in THF)[a]	No reaction
TBAF (1 M solution in THF)	Decomposition
NaOMe (25 wt. % solution in MeOH)	Formation of side products
t-BuOK (1 M solution in THF)	Acceptable conversion
NaOEt (30 wt. % solution in MeOH)	Formation of side products
KOEt (solution in THF)[a]	No reaction
LiOEt (1 M solution in THF)	Clean conversion

From the tested bases, $NaNH_2$, NaH, KF and KOEt did not show any reactivity towards **20** which is most probably due to their low solubility in THF. In the case of the fluoride base TBAF, there is no differentiation between P-P and P-C bonds leading to complete decomposition. The remaining bases, NaOMe, NaOEt, LiOEt, and *t*-BuOK yield metallated phosphanylphosphonate **21**. In the case of the sodium bases NaOMe and NaOEt reaction monitoring by ^{31}P NMR spectroscopy suggested that the alkoxides primarily attack the trivalent P-atom resulting in formation of $Mes^F\text{-}P(OEt)_2$ and $Mes^F\text{-}P(OMe)_2$, respectively. Using the bulky *t*-BuOK base gives an acceptable conversion with some small amounts of side products. The best results were obtained when using a THF solution of LiOEt. This reaction proceeds very fast and can be followed by a color change of the solution from yellow to deep red. After cleavage of the P-P bond, intermediate **21** is formed quantitatively. In the final step, which is accompanied by decoloration of the solution, protonation of **21** by anhydrous HCl (solution in Et_2O) affords phosphanylphosphonate **15**. The crude mixture is purified by column chromatography to yield a colorless oil that crystallizes at -20 °C. During the work-up and purification, significant amount of the phosphanylphosphonate decomposes which might explain a very low isolated yield of 11%. The main decomposition product was identified as 2,4,6-tris(trifluomomethyl)phenylphosphinic acid that arises from the acid catalyzed hydrolysis of **15** at the trivalent P-center. The decomposition product exhibits a characteristic doublet signal at $\delta_{31\mathrm{P}} = 15.7$ ppm with a strong P-H coupling constant $^{1}J_{\mathrm{P\text{-}H}} = 614$ Hz in the ^{31}P NMR spectrum. While phosphanylphosphonate **15** is sensitive towards hydrolysis, it can be stored under a nitrogen atmosphere at low temperatures for several weeks. Both compounds **21** and **15** feature two characteristic doublets in their respective ^{31}P NMR spectrum. **15** shows a doublet signal at $\delta_{31\mathrm{P}} = 29.0$ ppm and a doublet of septet at $\delta_{31\mathrm{P}} = -98.6$ ppm with $^{1}J_{\mathrm{P\text{-}P}} = 170$ Hz and $^{4}J_{\mathrm{P\text{-}F}} = 28.9$ Hz. In comparison to the corresponding Mes* variant ($^{1}J_{\mathrm{P\text{-}P}} = 222$ Hz)[97b] the P-P coupling constant is much smaller. Since $^{1}J_{\mathrm{P\text{-}P}}$ increase with the bond order between the two phosphorus atoms, the smaller $^{1}J_{\mathrm{P\text{-}P}}$ in **15** indicates that the Mes^{F} group weakens the P-P bond.[58a, 153] The same observation is found for the deprotonated form **21** where the metallated phosphanylphosphonate with Mes^{F} protecting group has a smaller coupling constant ($^{1}J_{\mathrm{P\text{-}P}} = 530$ Hz) than the Mes* analog ($^{1}J_{\mathrm{P\text{-}P}} = 615$ Hz).[97b] Consequently, the $\Delta\delta_{31\mathrm{P}}$ between the resonances of the P^{III} and P^{V} centers in **21** are significantly larger. Like the Mes* analog, also intermediate **21** is best described as the enolate form with a double bond character since the coupling constant is in the range of phosphoranylidenephosphines.[96a]

The structure of **15** was confirmed by X-ray diffraction analysis of single crystals obtained from slow evaporation of anhydrous *n*-hexane solution at -20 °C (*Figure 5.2*). **15** crystalizes in the monoclinic space group C 2/c as colorless blocks.

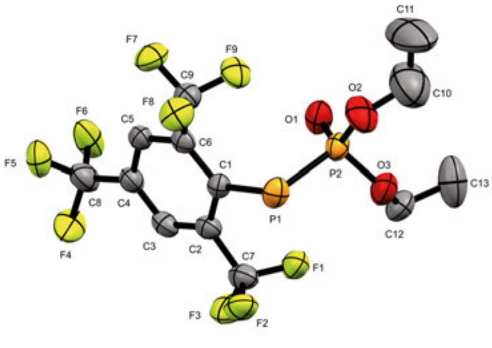
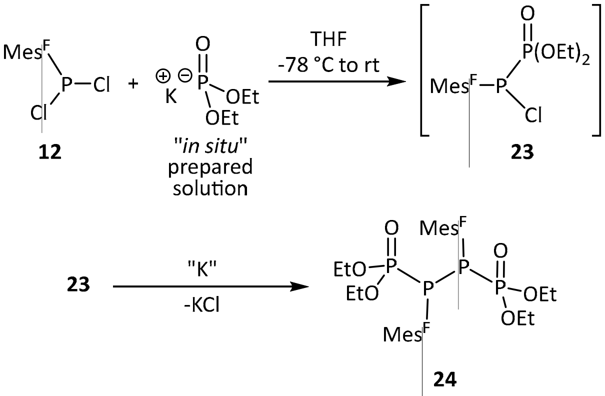


Figure 5.2 ORTEP representation of phosphanylphosphonate reagent **15** with 50% displacement ellipsoids. All hydrogen atoms are omitted for clarity. Selected bond length[Å] and angles [°]: C1-P1 1.860(6), P1-P2 2.211(2), P2-O1 1.449(7), P2-O2 1.561(5), P2-O3 1.578(5), C1-P1-P2: 98.8(2).

The P1-P2 distance of 2.211(2) Å in **15** is slightly elongated by 0.026 Å when compared to Mes*-protected phosphanylphosphonate. The C1-P1-P2 bond angle of 98.8(2)° in **15** is more obtuse compared to 96.6(6)° in the Mes* variant.[97b] The weakening of the P-P bond by the Mes^F group is due to its strong electron pulling effect which leads to less electron density between the two phosphorus atoms. This is also in agreement with the lower $^1J_{P\text{-}P}$ coupling constant discussed above. Otherwise, the structure of **15** has very high similarity to the corresponding Mes*-protected *phospha*-HWE reagent **1**.

5.2.3 Unexpected side reaction and product

During initial attempts to prepare compound **15** an interesting side product was obtained. After isolating in 16% yield, it was characterized as diphosphine-1,2-bisphosphonate **24** which is a linear dimer of phosphanylphosphonate **21**. A proposal for a possible pathway for the formation of **24** is outlined in *Scheme 5.4*.



Scheme 5.4 Proposed reaction sequence for the formation of side product **24**.

Most probably, after reaction of dichlorophosphine **12** with one equivalent of potassium diethylphosphite a transient monochlorinated species **23** is formed which can dimerize when traces of potassium are present. The presence of potassium is crucial for the formation of **24** since it was only observed in few cases when an *in situ* prepared solution of potassium diethylphosphite was employed. Potassium is known to be a powerful reducing agent and can reduce species **23**. The formation of a P-P bond is consistent with reduction chemistry and in principle, can possibly proceed *via* an ionic or radical mechanism.

Structural confirmation of **24** was ensured by X-ray diffraction analysis of single crystals obtained from slow evaporation of an anhydrous *n*-hexane solution at -20 °C (*Figure 5.3*).

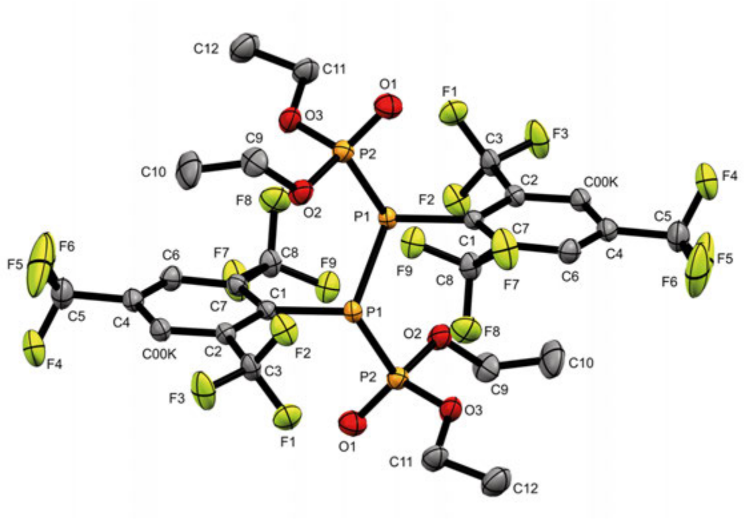
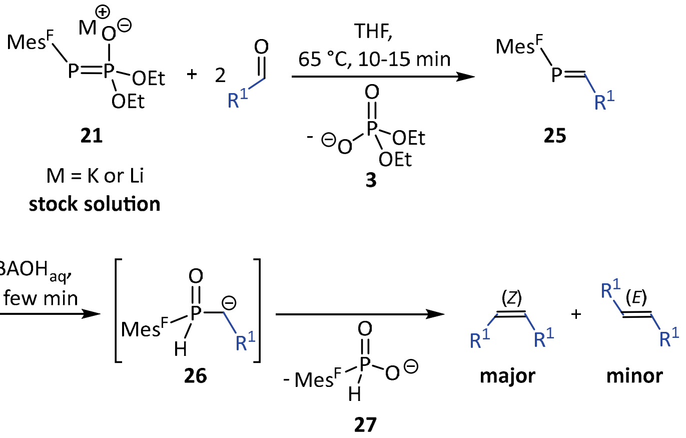


Figure 5.3 ORTEP representation of the crystal structure for tetraethyl(1,2-bis(2,4,6-tris(trifluoromethyl)phenyl)diphosphane-1,2-diyl)bis(phosphonate) (**24**) with 50% displacement ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond length [Å] and angles [°]: C1-P1 1.874(2), P1-P1 2.2232(9), P1-P2 2.2013(9), P2-O1 1.464(2), P2-O2 1.567(2), P2-O3 1.582(2), P2-P1-P1: 102.19(3).

Compound **24** crystallizes in the monoclinic space group $P\ 2_1/c$ as yellow cubes. The P1-P2 bond length of 2.2013(9) Å is slightly shorter than in the protonated phosphanylphosphonate **15**. The P1-C1 bond is 1.874(2) Å and 0.014 Å longer than in **15** which is due to a higher degree of steric repulsions in **24**. The internal P1-P1 bond is 2.2232(9) Å and longer than the P1-P2 bond which is again a result of steric repulsion. The dihedral angle between the two P2 atoms is exactly 180.0 °. Thus, all four P atoms are in the same plane and the two Mes^F groups are orthogonal to that plane since the dihedral angle between the two C1 atoms is also 180.0 °.

5.3 Reactivity towards aldehydes in a one-pot reaction

Since the reaction of the *phospha*-HWE reagent with an aldehyde is initiated by deprotonation of the P^{III} center in **15**, its preparation and isolation can be omitted. In fact, a stock solution of **21** is a more convenient starting material which is prepared in accordance with the procedure described in previous section 5.2.2 in *Scheme 5.3*. Under an argon atmosphere, **21** shows a good stability at room temperature, and can be stored for several days without significant decomposition. It is this stock solution that is used for the one-pot reductive aldehyde-aldehyde coupling reaction that is depicted in *Scheme 5.5*.



Scheme 5.5 General representation of the *Z*-selective reductive homo-coupling of two aldehydes using a stock solution of *phospha*-HWE reagent **21**. R^1 = aromatic, heterocyclic.

In a typical procedure, two equivalents of aldehyde are added to a solution of **21** at room temperature, and the mixture is heated up to 65 °C. After 10-15 minutes a phosphaalkene intermediate **25** is formed in a *phospha*-HWE reaction.[154] This step proceeds slower than in the corresponding phosphanylphosphonate **1** with Mes* protecting group since the electron withdrawing character of the Mes^F substituent decreases the nucleophilicity of the P^{III} center in **21**. In order to enhance the reactivity increased reaction temperatures are necessary. Quenching of **25** with a $TBAOH_{aq}$ solution at room temperature generates the phosphine oxide **26** *in situ* that immediately reacts further with the second equivalent of aldehyde under alkene formation. The nucleophilic attack of the hydroxide ion at the P=C bond and subsequent coupling of **26** with the aldehyde are faster in comparison to the reaction with non-fluorinated reagent **1** from chapter 3. This can be attributed to the increased electrophilicity of the P center as well as higher acidity of the α-proton in the phosphine oxide **26**. The swiftness of the reaction gives rise to the irreversible formation of the kinetic olefin product, which indeed was observed, since *Z*-alkenes are formed as the major isomer (*Scheme 5.5*). The stereochemical outcome is under reagent control and solely due to the presence of the Mes^F group in **21**. A clear indication for this is the fact that the analogous coupling with Mes* reagent **1** under identical conditions is 100% *E*-selective (chapter 3).

It is important to emphasize at this point that the coupling step from phosphaalkene to alkene is performed at room temperature. This is not the case for most *Z*-selective modifications of the HWE reaction, where low temperatures are required in order to stabilize the kinetically more favored *Z*-isomer. There are only some rare examples of such olefinations that are performed at temperatures higher than 0 °C.[143]

The phosphorus and fluorine centers in the coupling reagent allow to follow the reaction progress by ^{31}P and ^{19}F NMR spectroscopy. A representative example is shown in *Figure 5.4* for the homo-coupling of benzofuran-2-carboxaldehyde.

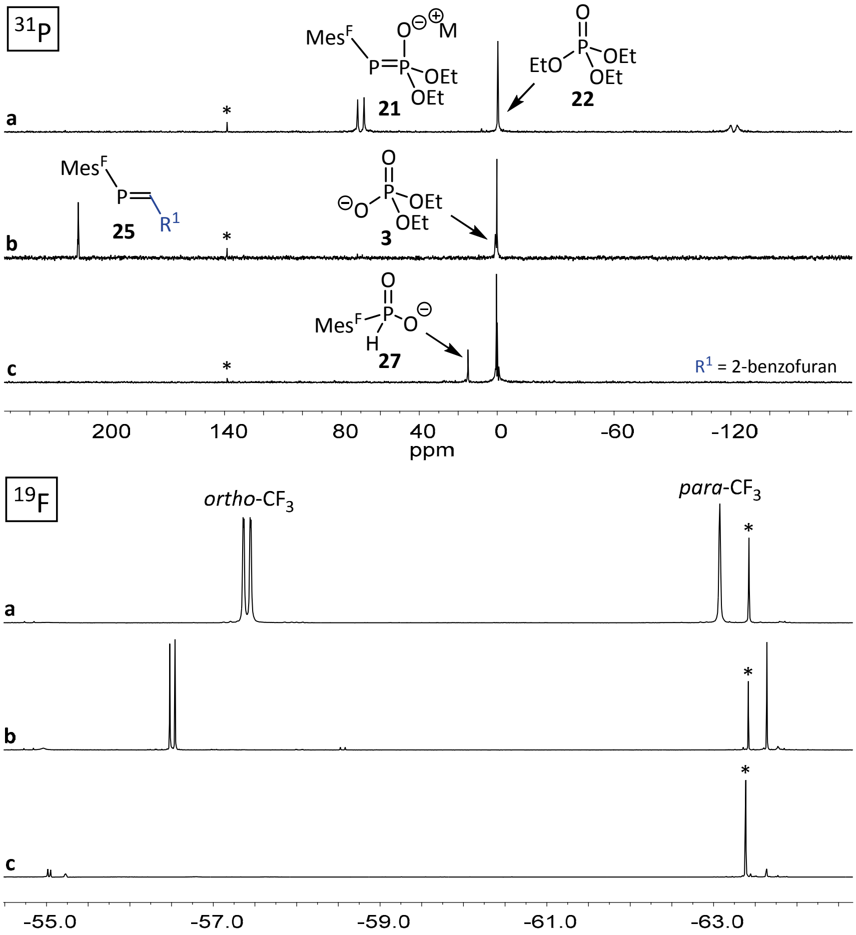


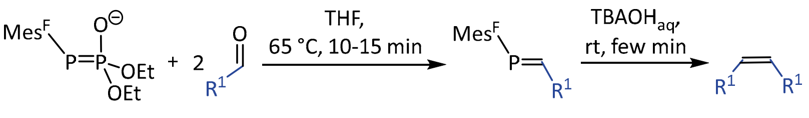
Figure 5.4 ^{31}P NMR spectroscopic monitoring of the reaction sequence (top). Corresponding ^{19}F NMR spectra (bottom). * Mes^{F}P(OEt)$_2$ as side product that is formed during dephosphorylation of bis(diethylphosphoryl)phosphine **20**.

In the first step (a → b), anionic phosphanylphosphonate **21** from the stock solution reacts with one equivalent of the aldehyde to yield the corresponding phosphaalkene **25** (215 ppm in ^{31}P NMR (C_6D_6) spectrum). Quenching with TBAOH$_{aq}$ solution rapidly consumes **25** and leads to formation of the olefinic product (b → c). This step is accompanied by the generation of the Mes^F containing phosphinate by-product **27**. The corresponding signals for **21** in ^{19}F NMR (C_6D_6) spectrum are a broad singlet and a doublet of doublets. The two *ortho*-CF_3 moieties couple with both phosphorus atoms with typical coupling constants of $^4J_{F\text{-}P} = 31.4$ Hz and $^5J_{F\text{-}P} = 4.5$ Hz. The phosphaalkene intermediate **24** has a doublet signal with a coupling constant $^4J_{F\text{-}P} = 23.5$ Hz (*ortho*-CF_3) and a singlet (*para*-CF_3) signal.

5.4 Substrate scope

With a reliable protocol for the preparation of the reagent **21** and the coupling sequence (*Scheme 5.3* and *5.4*) in hand, the reactivity towards aldehydes and the reaction scope were investigated. In general, the scope is limited to the use of electron poor aldehydes due to a decreased nucleophilic character of the P^{III} center in **21**. Therefore, the initial study of the substrate scope mainly focuses on electron deficient aromatic and heterocyclic aldehydes. Electron rich aldehydes are not suitable, since in such case the formation of phosphaalkene intermediates is less efficient leading to decompositions and side products.

5.4.1 Symmetrical *Z*-alkenes from homo-couplings

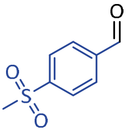
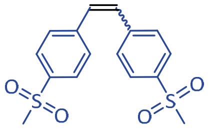
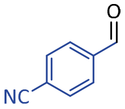
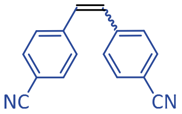
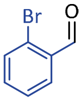
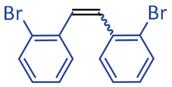
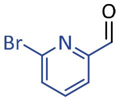
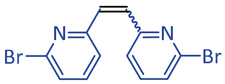
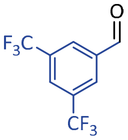
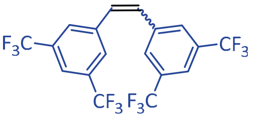
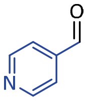
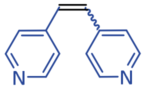
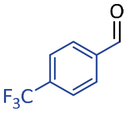
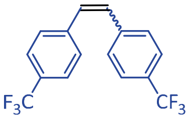
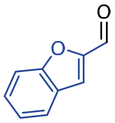
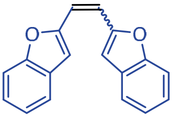


21 **25**

Overall, the direct aldehyde-aldehyde homo-coupling proceeds well with good yields for all tested aromatic and heterocyclic aldehydes (*Table 5.2*). For most substrates some unreacted aldehyde can be recovered resulting in conversions of 50-75%. The coupling tolerates substituents in *ortho*, *meta*- and *para*-positions.

Interesting to note is that phosphaalkenes with strongly EWG display an increased reactivity. In the case of 4-methylsulfonylbenzaldehyde and 4-cyanobenzaldehyde (Entry 1 and 2 in *Table 5.2*), the phosphaalkenes are not stable under the given basic reaction conditions, and rapidly react all the way to the respective olefins. For those aldehydes the homo-coupling does not require addition of $TBAOH_{aq}$ and the corresponding phosphaalkene intermediates were not observed during reaction monitoring *via* ^{31}P-NMR spectroscopy.

Table 5.2 Reaction scope for the reductive aldehyde-aldehyde homo-coupling with corresponding *E*/*Z* product ratios and ^{31}P NMR chemical shifts of phosphaalkene intermediates. Isolated yields refer to one equivalent of aldehyde. [a]Conversions refer to reacted amount of aldehyde.

Entry	**Aldehyde**	**Product**	**Isolated yield (Conversion)[a] [%]**	***E*/*Z* product ratio [%]**	**Chemical shifts δ_{31P} of P=C intermediate [ppm]**
1			40 (67)	9 : 91	---
2			45 (49)	10 : 90	---
3			46 (61)	20 : 80	230
4			60 (60)	23 : 77	248
5			59 (59)	28 : 72	240
6			51 (59)	30 : 70	244
7			41 (47)	47 : 53	233
8			44 (74)	58 : 42	215

The *E*/*Z* ratio of the products is not fully controlled by the reagent, but also depends to some extend on the electronic nature of the aldehyde. A general trend in *Table 5.2* shows that aldehydes with more electron deficient character give rise to higher ratios of *Z*-isomer. Moreover, the percentage of the *Z*-isomer shows a linear correlation with the ^{31}P NMR chemical shift values δ_{31P} of the corresponding phosphaalkene intermediates. This is evidenced by a linear regression fit in *Figure 5.5* (depicted as red line). The tendency is that phosphaalkenes with higher downfield shifts and thus, more deshielded P center result in olefins with higher *Z*-isomeric ratios.

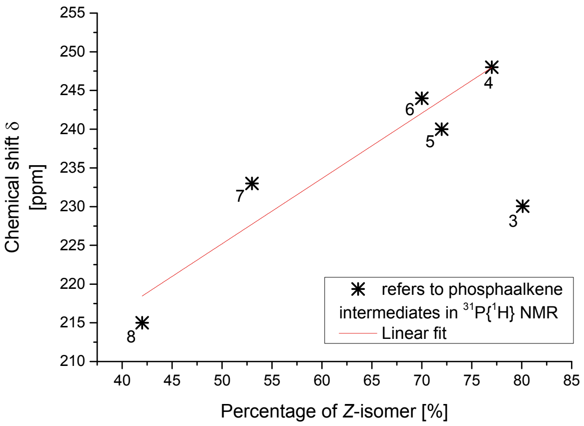
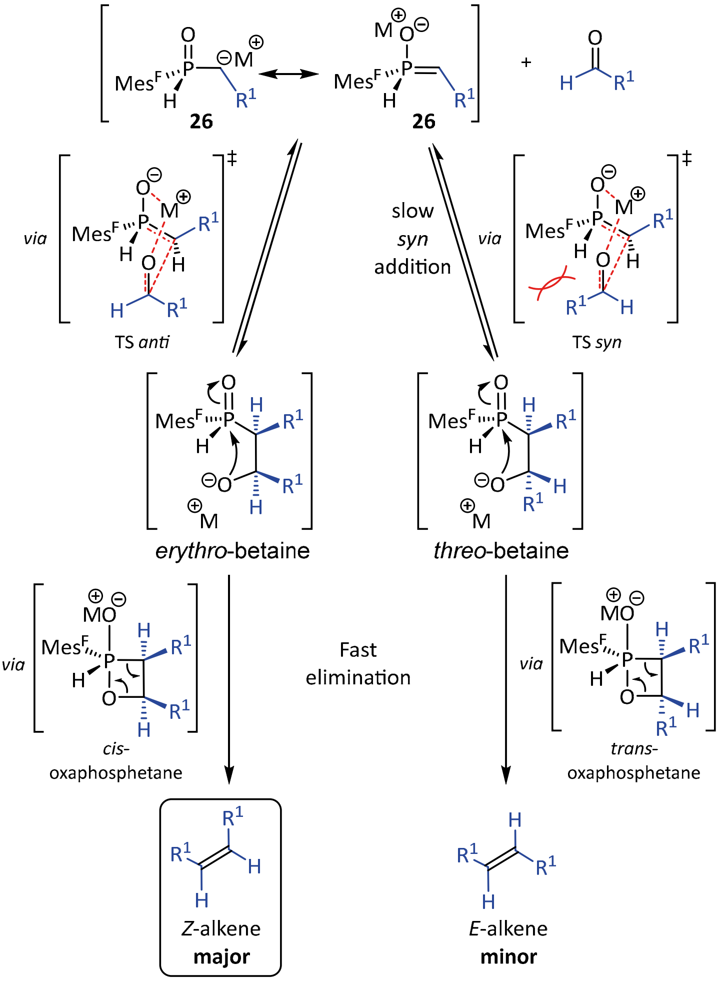


Figure 5.5 Correlation between chemical shift values δ_{31P} of phosphaalkene intermediates and the percentage of *Z*-isomer of olefinic products. Numbers indicate the entries from *Table 5.2*. The value from entry 3 is not included in the linear regression.

This analysis is in agreement with increased electrophilicity of the P center in electron poor phosphaalkenes leading to faster reactions and higher amounts of the kinetic *Z*-product. Only in case of *ortho*-bromobenzaldehyde (Entry 3, *Table 5.2*) the linearity is disrupted. A large amount of *Z*-alkene is obtained despite relatively low ^{31}P NMR chemical shifts of the corresponding phosphaalkene. This might be due to an *ortho*-effect that has been described by the group of GILHEANY *et al.* which showed that *ortho*-substituted aldehydes can yield unusually high *Z*-selectivity in WITTIG-type olefinations.[155]

5.5 Mechanistic aspects on stereochemical outcome

For a better understanding and explanation of the high *Z*-selectivity it is important to carry out investigations into mechanistic details. From the overall reaction it is clear that the stereochemical outcome is determined in the last step of the sequence which is the reaction between the phosphine oxide **26** and a second equivalent of aldehyde. Since the active reagent is a phosphine oxide, the coupling follows a HW-type mechanism. This bears analogy to the cross-coupling described in chapter 3 where the reaction is 100% *E*-selective when the P substituent is a Mes*. By changing to Mes^F the selectivity is reversed. Consequently, the mechanistic discussion is in accordance to the STILL-GENNARI modification and includes aspects from both HW and HWE olefinations. A proposed detailed mechanism is depicted in *Scheme 5.6*.


26
26
via
TS anti
slow
syn
addition
via
TS syn
erythro-betaine
threo-betaine
via
cis-
oxaphosphetane
Fast
elimination
via
trans-
oxaphosphetane
Z-alkene
major
E-alkene
minor

M = Li, K, tetrabutylammonium
R^1 = electron-deficient aromatic or heterocyclic

Scheme 5.6 Proposed mechanism for *Z*-selective aldehyde-aldehyde homo-coupling in accordance to STILL-GENNARI modification and with close similarity towards HW reaction.

In general, the stereochemistry of all WITTIG-type olefinations depends largely upon the relative orientation of the R^1-groups in the OPA intermediate. In HW as well as STILL-GENNARI variation the initial addition of the olefinating reagent into the aldehyde is relatively slow. Due to less steric repulsion in the transition state (TS), the *anti*-addition is faster and therefore preferentially compared to the formation of the *syn*-adduct. Once the addition occurred, the subsequent steps are fast. This is a result of the strong electron withdrawing character of the Mes^F group that increases the electrophilicity of the P center and thereby facilitates the formation of *cis*-OPA. The latter is formed despite steric repulsions between the R^1-groups, and since the intermediate species are sufficiently short lived, a fast and irreversible elimination yields the *Z*-alkene as dominating product. Additionally, the irreversible collapse of the OPA is supported if R^1-groups have electron withdrawing character. Such a reactivity pattern makes the aldehyde addition the rate determining step (RDS) allowing the formation of the kinetic alkene product. This is different to the reaction of the Mes* analog which mechanism was discussed in detail in section 3.7 (*Scheme 3.15*). In that case, the formation of the OPA is RDS and the equilibrium between the *syn*- and *anti*-addition gives rise to the thermodynamically more favored *trans*-OPA and *E*-alkenes.

5.6 Conclusions

A reliable synthetic protocol for the preparation of a novel metal-free *phospha*-HWE reagent bearing an electron poor Mes^F protecting group was developed. The synthesis from Mes^F-dichlorophosphine starting material is performed on gram-scale in a one-pot reaction to yield a stock solution of the reagent which is applied to reductive homo-couplings of aromatic and heterocyclic aldehydes. Initial investigations of the reaction scope demonstrate first literature examples where two aldehydes are coupled under transition metal-free conditions to alkenes with high *Z*-stereoselectivity. Hence, the stereochemistry of the product can be tuned by modifying the electronic properties of the protecting group. The methodology presented offers significant advantages over the known MCMURRY reaction from a stereochemical viewpoint. Also in comparison to WITTIG- and HWE-type reactions this methodology is beneficial in the fact that the preparation of highly functionalized ylide/phosphonate precursors is omitted.

6. Reducing steric bulk on phosphaalkenes – equilibria studies of triphenylphosphaalkenes (Paper IV)

This chapter briefly describes reactivity and stability studies of phosphaalkenes that are lacking steric protection by bulky substituents. A modified synthetic procedure for triphenylphosphaalkenes with different *para*-substituents at the C-phenyl groups and investigations on the chemical equilibria of the corresponding monomeric, dimeric and oligomeric species are presented.

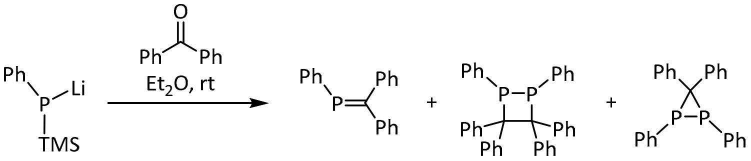
6.1 Introduction

As mentioned in chapter 4, another strategy to enlarge the substrate scope for the reductive coupling of aldehydes to alkenes is to reduce the steric bulk of the protecting group on the intermediate phosphaalkenes. But decreasing the steric bulk results in lower kinetic stabilization of the phosphaalkenes and synthetic challenges.[80c] This is exemplified by the fact that phosphaalkenes with smaller protecting groups such as mesityl (Mes)[82g] are fewer in the literature compared to those with bulky groups such as supermesityl (Mes*).[77b, 86a, 97b, 156] Phosphaalkenes with *P*-phenyl groups are even less stable and rapidly dimerize to the corresponding 1,2-diphosphetanes.[102b] However, high reactivity is generally appealing if the phosphaalkenes are intermediates in downstream chemical transformations like in the case of the one-pot aldehyde couplings.

To better estimate the stability and reactivity of phosphaalkenes with low kinetic stabilization, a series of triphenylphosphaalkenes with different electronic properties were prepared, and their dimerization and oligomerization behavior was investigated. Such a fundamental study on chemical equilibria of the triphenylphosphaalkenes is the basis for its potential application in the reductive carbonyl-to-alkene coupling chemistry.

6.2 Synthesis of triphenylphosphaalkenes

Current synthetic protocols to *P*-phenylphosphaalkenes[102b] are somewhat unreliable and suffer from irreproducibility and the formation of various undesired side products. Typically, the *P*-phenylphosphaalkenes are prepared in a *phospha*-PETERSON reaction.[82g, 83b] The starting material PhP(Li)TMS **28** is made *in situ* by treating $PhP(TMS)_2$ with one equivalent of MeLi in THF, and then **28** is reacted with ketones to afford the corresponding phosphaalkenes.[102b] This procedure is plagued by the formation of side products which might stem from reactions of small amounts of unreacted MeLi or other organolithium products. In particular, polymeric side products can be formed as it is known that MeLi initiates anionic polymerization of phosphaalkenes.[126, 157] To overcome this undesired reactivity, MeLi can be replaced by LiOEt as desilylating agent.[158] In our modified protocol PhP(Li)TMS is prepared by the addition of one equivalent of a LiOEt solution in THF to $PhP(TMS)_2$ at room temperature. Removal of the solvents yields a yellow solid that is dissolved in anhydrous Et_2O and used as starting material for the preparation of *P*-phenylphosphaalkenes. Addition of benzophenone to the ethereal solution of **28** generates a mixture of three phosphorus-containing species which is in analogy to a report by GATES *et al.*[102b] This mixture consists of the desired phosphaalkene **29a**, its head-to-head dimer **30a**, and a diphosphirane **31a** (*Scheme 6.1*).

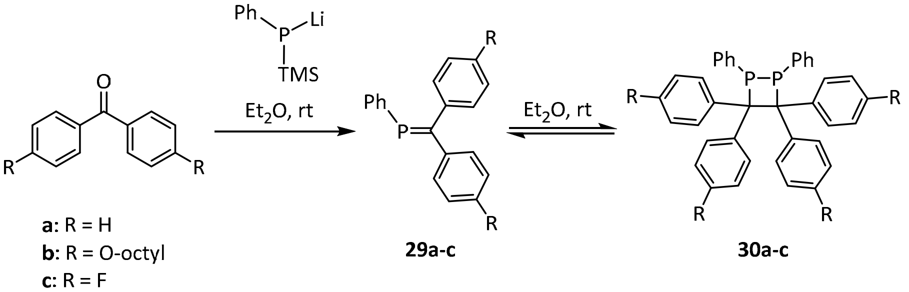


28 **29a** **30a** **31a**

Scheme 6.1 Reaction of PhP(Li)TMS with one equivalent of benzophenone resulting in a product mixture of **29a**, **30a**, and **31a**. An ethereal solution of benzophenone is added to a solution of PhP(Li)TMS in anhydrous Et_2O.

^{31}P NMR spectroscopic monitoring of the reaction revealed that **29a** and **30a** are in equilibrium while **31a** is formed as a side product the concentration of which remains constant. Diphosphirane **31a** origins from a nucleophilic attack of **28** on the phosphaalkene **29a**. This hypothesis was tested in a reaction between two equivalents of **28** and one equivalent of benzophenone. Using this stoichiometry resulted in an immediate and quantitative formation of **31a**. During the reaction, the transient phosphaalkene **29a** is attacked by the second equivalent of **28** and transformed into the diphosphirane **31a**. The formation of **31a** can be suppressed by simply reversing the order of addition of the two reagents. Thus, the addition of one equivalent of PhP(Li)TMS **28** to the ethereal benzophenone solution gives solely the phosphaalkene **29a** which is in equilibrium with its dimer **30a**.

With a reliable and high-yielding synthetic procedure in hand, two other triphenylphosphaalkenes that carry either an EDG (**29b**) or EWG (**29c**) in the *para*-positions of their *C*-phenyl groups were prepared (*Scheme 6.2*). For the reaction with PhP(Li)TMS ketone **b** (R = O-octyl) and **c** (R = F) were used.



Scheme 6.2 Synthesis of phosphaalkenes **29a-c** from **28** and benzophenones with different *para*-substituents, followed by dimerization equilibrium to form 1,2-diphosphetanes **30a-c**.

6.3 Investigations on dimerization processes of triphenylphosphaalkenes

The three ketones **a-c** mainly differ in their reactivity towards PhP(Li)TMS **28** since the electron deficient ketone **c** is expected to be more reactive than the electron rich analog **b**, and the unsubstituted benzophenone **a** being in between. Furthermore, the varying polarity of the subsequently formed P=C bonds will affect the stability of the phosphaalkenes **29a-c**. The reactions were monitored by ^{31}P NMR spectroscopy with an internal standard in order to get quantitative information (*Figure 6.1*). Mes*-phosphaalkene (*E*)-(4-methoxybenzylidene) (2,4,6-tri-*tert*-butylphenyl)phosphane was chosen as internal standard since it has high chemical stability and similar relaxation time as phosphaalkenes **29a-c**. Reaction monitoring by ^{31}P NMR spectroscopy revealed that the concentration of the phosphaalkenes **29a-c** slowly decreases owing to their head-to-head dimerization to **30a-c** (a → b → c in *Figure 6.1*). This reaction reaches a steady state concentration of both compounds after hours or days depending on the substituents R. For example, **29a** and **30a** (R = H) equilibrate with a 1:2.4 ratio after 48 hours (c in *Figure 6.1*). The reactions of **b** and **c** showed that electron donating substituents favor the phosphaalkene while in the opposite case with electron poor phenyl groups, the equilibrium is shifted towards the dimer. The results for the dimerization studies are summarized in *Table 6.1*.

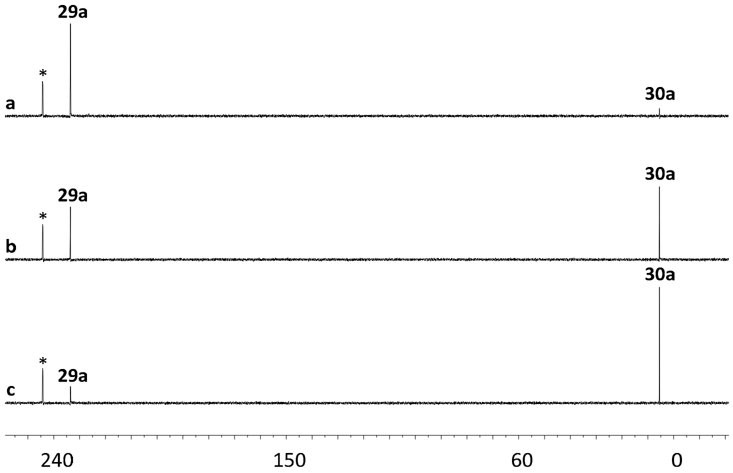
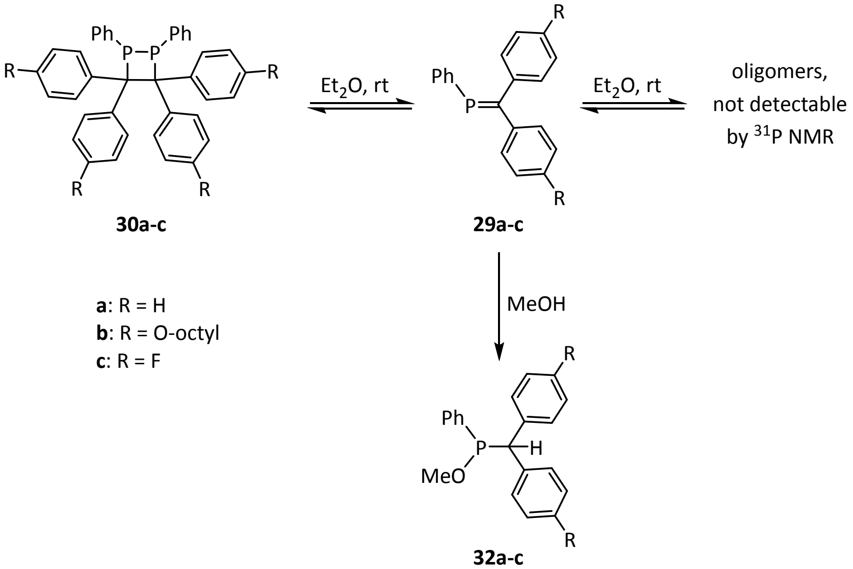


Figure 6.1 ^{31}P NMR investigation of the equilibrium between **29a** (δ_{31P} = 233 ppm) and **30a** (δ_{31P} = 5 ppm) a) First measurement after 14 minutes, b) after 2 hours and c) after 48 hours. *Internal standard (δ_{31P} = 244 ppm).

The use of the internal standard revealed another interesting feature of the reactivity of **29**. It was noticed that during the equilibration process the total amount of phosphorus species decreased markedly. Consequently, a second process is present which consumes some of the phosphaalkene but is not detectable by ^{31}P NMR. This process was assigned to be the formation of higher oligomers or polymers of **29** (*Scheme 6.3*).



Ph
Ph
P–P
R
R
R
R
Et2O, rt
Ph
P
R
R
Et2O, rt
oligomers,
not detectable
by 31P NMR
30a-c
29a-c
a: R = H
b: R = O-octyl
c: R = F
MeOH
R
Ph
P
H
MeO
R
32a-c

Scheme 6.3 Proposed equilibria between phosphaalkenes **29a-c**, 1,2-diphosphetanes **30a-c** and higher oligomers and their reaction with MeOH.

Since the concentration of **29** and **30** does not deplete completely during the equilibration process, we hypothesized that the formation of the oligomers is not irreversible but in chemical equilibrium with **29** and **30**. If this is correct, according to LE CHATELIER's principle all phosphorus species should be recovered in an irreversible quenching experiment that removes **29** from all equilibria. It was decided to use methanol as a suitable trapping reagent since it can irreversibly add across the P=C double bond. Hence, after reaching the equilibrium between **29** and **30**, methanol was added to the reaction mixtures (*Scheme 6.3*). The reaction monitoring after addition of methanol to the equilibrium between **29a** and **30a** is shown in *Figure 6.2*. As expected, a fast addition of methanol across the P=C double bond in **29a-c** yields the corresponding phosphinites **32a-c** (a in *Figure 6.2*). First, the dimers **30a-c** are not affected, but on a longer timescale (hours to days) they are converted into the phosphinites through their equilibrium with **29a-c**. The concentration of phosphinites **32a-c** increases and reaches a final maximum within a few days (c in *Figure 6.2*).

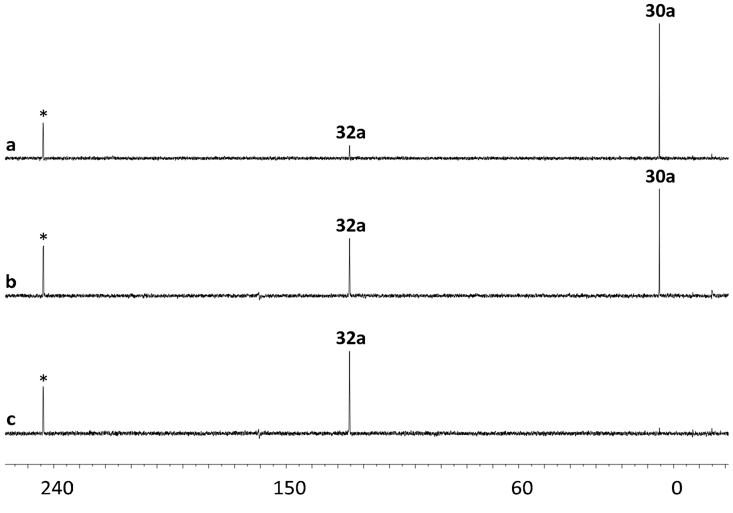


Figure 6.2 ^{31}P NMR investigation of the equilibrium between **29a** and **30a** after addition of MeOH leading to formation of **32a** (δ_{31P} = 125 ppm). First measurement after several minutes, b) after 30 hours and c) after 7 days. *Internal standard (δ_{31P} = 244 ppm).

The final concentration of **32a-c** (*Table 6.1*) corresponds actually to the yield of the initial *phospha*-PETERSON reaction as the reaction of methanol with the phosphalkenes is expected to be quantitative. Such an analysis discloses a remarkably high yield for the formation of phosphaalkenes **29a** and **29b** (87 and 73%, respectively). In the case of the electron poor benzophenone **c**, the yields are lower (54%) which is ascribed to the generally high reactivity of such ketones. Comparing these yields with the ones obtained by ^{31}P NMR analysis shortly after the formation of the phosphaalkenes shows only small deviations (*Table 6.1*). Thus, dimerization and oligomerization are slow processes in comparison to the phosphaalkene formation, but nevertheless reversible. This finding is essential for the potential use of triphenylphosphaalkenes as intermediates in the reductive carbonyl-to-alkene coupling chemistry.

Table 6.1 Results from investigations of equilibria between **29a-c**, **30a-c** and higher oligomers. [a]Yields determined using Mes*-phosphaalkene as internal standard.

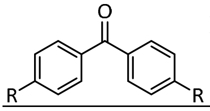
	**NMR yield of 29a-c[a] [%]**	**NMR yield of 32a-c[a] [%]**	**29a-c at equilibrium [%]**	**30a-c at equilibrium [%]**	**Oligomers at equilibrium [%]**
a: R = H	97	87	18	45	37
b: R = O-octyl	65	73	64	17	19
c: R = F	40	54	14	31	55

Table 6.1 summarizes the results from the quantitative analysis of all species in equilibrium, i.e. the phosphaalkenes **29a-c**, their dimers **30a-c** and oligomers that are not detectable by ^{31}P NMR spectroscopy. The analysis shows that electron deficient phosphaalkenes are most prone to oligomerization while electron rich phosphaalkenes exist mostly in their monomeric form. Such a reactivity trend is in agreement with the reactivity of Mes*-phosphaalkenes that were described in the previous chapters.

6.4 Conclusions

The modified *phospha*-PETERSON reaction enables a clean formation of different triphenylphosphaalkenes **29a-c** from PhP(Li)TMS **28** and unsubstituted (**a**) as well as electron rich (**b**) and electron deficient (**c**) benzophenones. The phosphaalkenes engage in chemical equilibria with the head-to-head dimerization to **30a-c** and oligomeric species that are not detectable by ^{31}P NMR spectroscopy. The electronic nature of the corresponding phosphaalkene influences the chemical equilibria. In general, electron rich phosphaalkenes favor the monomeric side whereas electron deficient phosphaalkenes are mainly in the oligomeric form. The mixtures of phosphaalkenes **29a-c**, their dimers **30a-c** and oligomers can be channeled into phosphinites **32a-c** by the irreversible quenching with methanol which adds across the P=C double bond. This reactivity shows that despite poor kinetic stabilization *P*-phenyl phosphaalkenes are stable enough to be used as intermediates in subsequent chemical transformations such as the conversion into phosphinites **32a-c**. The phosphinites are potentially valuable intermediates which can be oxidized to phosphinates and applied in a similar sequence of the reductive one-pot carbonyl coupling chemistry described in chapter 4.

7. Outlook

The reductive aldehyde coupling to alkenes is a new method, and despite the encouraging results from the first presented modifications; there are many aspects that can be addressed for further improvements.

First of all, the manipulation of the protecting group of the phosphaalkene intermediates has an enormous influence on the outcome of the reaction. For instance, it can change the *E*/*Z*-isomeric ratio of the product as it was shown in chapter 5. In this context, other protecting groups such as 2,4,6-trifluorophenyl or perfluorophenyl are expected to have a substantial impact on the electronic properties of the intermediates and thus, the stereochemical outcome of the reaction. In addition, it is interesting to investigate the effect of the temperature on the *E*/*Z*-isomeric ratio. Low temperatures might increase the selectivity towards the kinetic *Z*-alkene product since most of the Z-selective olefinations reported in the literature are typically performed at -78 °C.[143, 146, 148a, 148b, 159] Another approach is the reduction of steric protection on the phosphaalkene by using less bulky protecting groups such as mesityl (Mes) and phenyl (chapter 6) instead of Mes*. This gives more reactive intermediate species and enables a broader substrate scope regarding the type of the carbonyl functionality that can be coupled.[158]

The nucleophile for the activation of the P=C bond in phosphaalkenes is a further component that can be altered. For example, Grignard reagents such as EtMgBr or organolithium species such as *n*-BuLi can be used as alternative nucleophiles. An attack of *n*-BuLi on phosphaalkenes followed by oxidation would result in tertiary phosphine oxide intermediates which can probably undergo the coupling step.

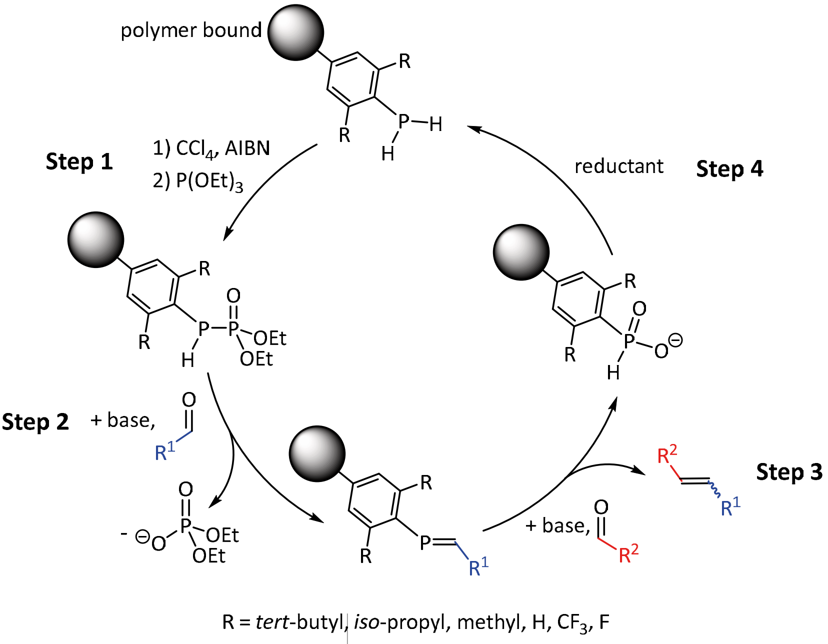
An interesting aspect is the modification of the reaction conditions and what effect an application of microwave irradiation and ultrasonication would have. The amount of solvent can be manipulated as well. From an environmental point of view, the reduction of the amount of solvent has become an issue in running reactions.[160] In this context, a biphasic medium is benefiting as it would allow an easier mode of separation where the alkenes are soluble in the organic phase while the organophosphorus by-products remain in the aqueous phase.

In this thesis, only 1,2-disubstituted alkenes were discussed. A logical continuation is the development of the new method for the preparation of tri-, tetrasubstituted and terminal alkenes. To achieve this goal, the coupling has to be extended towards the use of ketones as substrates. In particular, the preparation of tetrasubstituted alkenes is very challenging and a hot topic in synthetic organic chemistry as there have been very few reports on this process.[161] The preparation of terminal alkenes can potentially be realized with the described reaction conditions by using a commercial formaldehyde solution (e.g. formalin) in combination with $TBAOH_{aq}$ for the activation of the phosphaalkene intermediate and subsequent coupling. Such formaldehyde solutions are used in WITTIG reactions for the preparation of terminal alkenes.[162]

The application of the reductive carbonyl coupling towards the synthesis of macrocyclic systems and polymers is another exciting aspect. This can be achieved by using starting materials with two aldehyde functionalities in one molecule. For instance, benzene-1,4-dicarboxaldehyde can be employed in polymerization reactions, and macrocycles are accessible *via* intramolecular couplings in which the formation of the C=C double bond is a ring closing reaction.

Like all WITTIG-type olefinations, also the new method suffers from poor atom economy of the reaction. From an environmental and economic point of view, the organophosphorus by-products are valuable and should not be treated as waste. They may be recovered in similar procedures that are applied for the reductive recycling of phosphine oxides, phosphinates, and phosphonates to phosphines[160, 163] which can be reused for the preparation of the coupling reagents. With such an approach, catalytic versions of the WITTIG[164] and APPEL[165] reactions were developed. These reactions use Ph_2SiH_2 for the chemoselective reduction of the phosphine oxide by-product to regenerate phosphine.

A further possibility for a simple way to recover the by-products is the use of polymer bound or on silica or alumina adsorbed reagents. WITTIG- and HWE-olefinations with polymer bound reagents are known.[166] A similar strategy could be applied to the reductive aldehyde coupling. A proposed cycle for the reaction with polymer supported coupling reagent is represented in *Scheme 7.1*. This protocol can be used in a flow reactor. In the first step, the phosphanylphosphonate reagent is prepared on a surface bound to a polymer. The second step is the reaction with the first aldehyde to form the phosphaalkene intermediate. After the coupling (step 3) the olefinic product is released from the polymeric backbone while the phosphorus by-product remains bound to the surface. Simple removal of the product solution and washing of the polymeric surface would prepare the cycle for the last step; the reduction to the phosphine which regenerates the starting material for the next cycle.


polymer bound
Step 1
1) CCl_4, AIBN
2) $P(OEt)_3$
Step 2
+ base,
Step 3
+ base,
Step 4
reductant
R = *tert*-butyl, *iso*-propyl, methyl, H, CF_3, F

Scheme 7.1 Proposed cycle for the reductive aldehyde coupling with a polymer bound phosphanylphosphonate reagent.

A final goal is, of course, the application of the reductive aldehyde coupling in the preparation of more complex molecular systems and the synthesis of natural products. Hence, there is much potential for the new method to become a versatile tool in organic chemistry for the formation of C=C double bonds.

8. Concluding remarks and summary

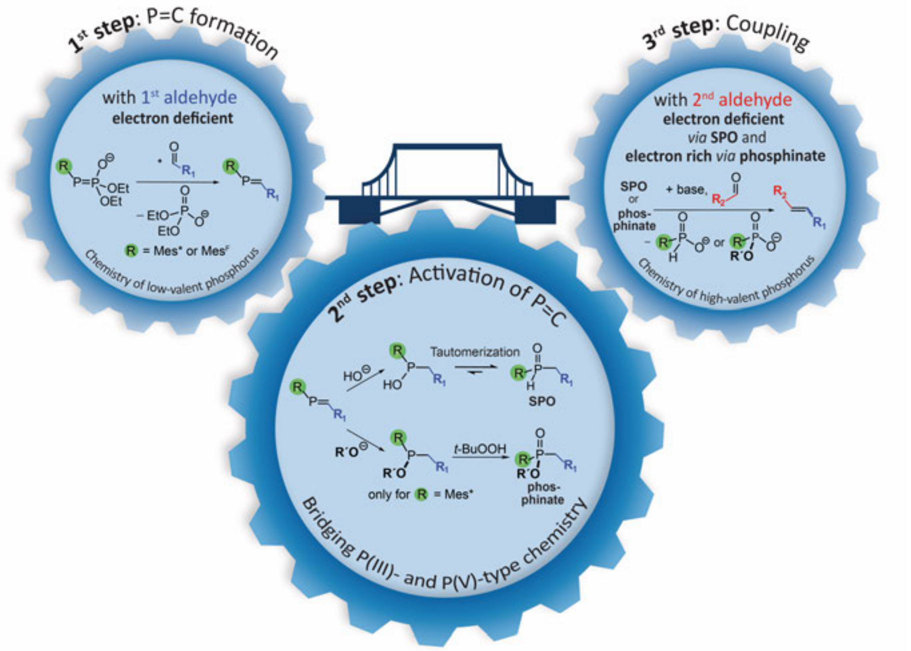
This thesis contributes to the field of carbonyl olefinations and is devoted to the development of a new synthetic methodology for an unprecedented one-pot reductive coupling of *two* aldehydes to alkenes. The coupling proceeds *via* $\lambda^3\sigma^2$ phosphaalkene intermediates which are formed from the reaction of aldehydes with phosphanylphosphonate reagents.

In comparison to the MCMURRY reaction, the new one-pot coupling method features several advantages. It is transition metal-free, benefits from mild conditions such as short reaction times and ambient temperatures, provides good yields and 100% *E*-alkenes when a Mes*-stabilized phosphanylphosphonate is used as reagent. However, most importantly it enables the formation of unsymmetrical alkenes from two dissimilar aldehydes while the MCMURRY reaction usually yields a mixture of the two symmetrical and the desired unsymmetrical products. The selectivity for the product formation in the one-pot reaction is due to a step-wise ionic mechanism.

A series of three individual steps enables a controlled addition of two different aldehyde substrates. In the first step, the Mes* phosphanylphosphonate reacts in a *phospha*-HORNER-WADSWORTH-EMMONS reaction with an aldehyde to form a phosphaalkene intermediate. This reaction is an example of an "Umpolung" as the polarity of the carbon center is changed from δ^+ in the aldehyde to δ^- in the phosphaalkene. In the second step, the phosphaalkene is activated by a nucleophilic attack of hydroxide and the resulting transient phosphinite species tautomerizes to a secondary phosphine oxide (SPO). In the third step, due to the basic reaction conditions the SPO undergoes an olefination with the second aldehyde yielding the olefinic product.[167]

In fact, the "activation" of the phosphaalkene is the main discovery and the key step in this new aldehyde-aldehyde coupling protocol. This base promoted step thus connects the chemistry of low-valent phosphaalkenes and the HORNER-WITTIG type carbonyl olefination chemistry of high-valent phosphine oxides by the *in situ* transformation of the phosphorus center from P^{III} into P^{V}. A general schematic overview for the complete coupling sequence with the base induced activation of the intermediate phosphaalkene and the subsequent olefination with the second aldehyde is depicted in *Scheme 8.1*.

In the initial proof-of-concept study the substrate scope was shown to be limited for the use of electron deficient aldehydes. For the second aldehyde the scope is somewhat broader and aromatic, heterocyclic, aliphatic, and vinylic systems are tolerated.


1st step: P=C formation
with 1st aldehyde
electron deficient
R
P=P
OEt
OEt
R1
– EtO–P
EtO
R = Mes* or MesF
Chemistry of low-valent phosphorus
3rd step: Coupling
with 2nd aldehyde
electron deficient
via SPO and
electron rich via phosphinate
SPO
or
phos-
phinate
+ base,
R2
R1
H
R'O
2nd step: Activation of P=C
HO⊖
HO
Tautomerization
SPO
R'O⊖
R'O
t-BuOOH
only for R = Mes*
phos-
phinate
Bridging P(III)- and P(V)-type chemistry

Scheme 8.1 Graphical representation of the one-pot reductive coupling of two aldehydes using phosphanylphosphonate reagents.

In order to broaden the substrate scope, the reaction sequence was modified. The addition of the hydroxide base was replaced by an alkoxide base followed by subsequent oxidation. This change results in an increased amount of oxygen substituent at the P-center leading to transient phosphinate intermediates which in comparison to the previous SPO display a higher reactivity towards electron rich benzaldehydes (*Scheme 8.1*). Hence, *trans*-stilbenes with push-pull electronic properties are directly accessible from the coupling of an electron poor and an electron rich aldehyde.

In a different approach, a modification of the stereochemical outcome of the coupling reaction was targeted. Inspired by the *Z*-stereoselective STILL-GENNARI olefination, that uses strong electron withdrawing substituents on the phosphonate reagents, a new phosphanylphosphonate reagent with the electron deficient Mes^{F} protecting group was synthesized and successfully implemented into the one-pot coupling reaction. Owing to the strong electron withdrawing effect of the trifluoromethyl groups a high ratio of the *Z*-isomer was achieved under the same reaction conditions as with the Mes*-stabilized phosphanylphosphonate reagent. Hence, by modifying the electronic properties of the protecting group the stereochemistry can be tuned. Initial investigations on the substrate scope showed first literature examples of reductive homo-couplings of aromatic and heterocyclic aldehydes to alkenes with high *Z*-stereoselectivity.

The last part of the thesis presents a further strategy for enlarging the substrate scope. The strategy is based on the reduced steric protection of the intermediate phosphaalkenes since such phosphaalkenes are known to be very reactive but at the same time prone to decomposition. To get insights into the reactivity and stability of phosphaalkenes with poor kinetic stabilization three different triphenylphosphaalkenes were prepared in *phospha*-PETERSON reactions between PhP(Li)TMS and unsubstituted, electron rich, and electron deficient benzophenones. Investigations showed that the triphenylphosphaalkenes are engaged in chemical equilibria processes, in which they can dimerize to the corresponding 1,2-diphosphetane and form higher oligomers or polymers. Depending on the electronic properties of the substituent on the C-phenyl groups either the dimerization and oligomerization or the monomeric form is favored. For electron-rich substituents, the equilibrium is more on the side of the monomer while with electron deficient substituents the phosphaalkenes are prone to dimerization and oligomerization. These processes do not occur immediately and need longer equilibration time. This means that in principle, triphenylphosphaalkenes are possible intermediates in downstream chemical processes like the described carbonyl-to-alkene coupling chemistry. Such an approach would most probably extend the substrate scope for the use of more different types of aldehydes and ketones and give rise to further improvements of the reductive one-pot carbonyl coupling reaction.

Svensk sammanfattning

Metoder för att kunna bilda kol-kol dubbelbindningar (C=C) och den kemi som rör alkener, är av stor betydelse för grundforskningen, så väl som den industriella utvecklingen, inom organisk kemi.[2] Detta beror framförallt på den stora förekomsten av C=C bindningar i biologiskt aktiva naturprodukter såsom lipider och vitaminer, samt syntetiska system såsom läkemedel, färgämnen och plaster.[3a] Upptäckten av nya metoder för att skapa C=C bindningar utgör därför en viktig del i utvecklingen av syntetisk kemi.

Av de metoder för bildning av C=C bindningar som, i dagsläget, finns publicerade i litteraturen, är det endast MCMURRY-reaktionen som kan användas för att reducera och koppla samman karbonylföreningar till alkener i en reduktiv karbonylkopplingsreaktion, även kallad reduktiv karbonylolefinering.[2f]

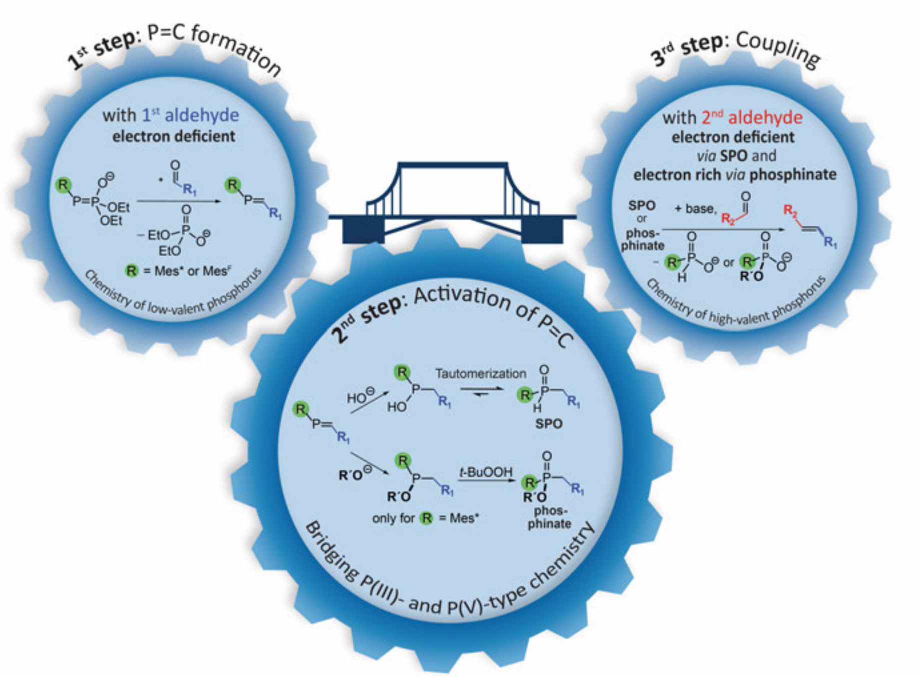
Den här avhandlingen fokuserar på utvecklingen av ett nytt syntesprotokoll, i vilket den reduktiva karbonylkopplingen av aldehyder till alkener sker i ett enda kärl. Denna så kallade enkärlsreaktion, har hämtat inspiration från den organiska fosforkemin eftersom organiska forsforreagens är allmänt kända för deras användbarhet inom just karbonylolefinering. Fosfoniumylider är de mest kända organiska fosforreagensen och upptäckten av dessa ledde till att GEORG WITTIG, år 1979, fick motta Nobelpriset i kemi.[168]

I de experiment som beskrivs i denna avhandling används reagenset Mes*P(H)P(O)(OEt)$_2$ – ett så kallat fosfonylfosfonatreagens med en skrymmande skyddsgrupp, 2,4,6-(*tert*-butyl)$_3$Ph, som här noteras Mes* – i en *fosfa*-variant av WITTIGs reaktion kallad *fosfa*-HORNER-WADSWORTH-EMMONS-reaktionen, för syntesen av fosfaalkener från aldehyder.[95a, 97b] Fosfaalkener är föreningar innehållandes en P=C bindning och dessa utgör viktiga intermediat i enkärlsreaktionen.

Det finns flera fördelar med enkärlreaktionen jämfört med MCMURRY-reaktionen. Den är bland annat fri från användandet av övergångsmetaller, äger rum under milda förhållanden och med korta reaktionstider, samt är stereoselektiv och resulterar i 100% *E*-alkener. Dess största fördel är dock att den möjliggör selektiv tillverkning av osymmetriska alkener medan MCMURRY-reaktionen vanligtvis ger en blandad kompott av symmetriska och osymmetriska produkter.[11, 24b, 24c]

Enkärlsreaktionens selektivitet är resultatet av en stegvis jonmekanism, där följden av tre separata steg möjliggör kontrollerad addition av två olika aldehydsubstrat. Låt oss föreställa ett exempel där vi vill kombinera substitutenter från två olika aldehyder – Aldehyd A och Aldehyd B. I det första steget, dvs.”Wittig-delen” av reaktionen där fosfaalkenintermediatet bildas, genomgår karbonylkolet i Aldehyd A en förändring i polaritet (Umpolung) från δ^+ till δ^-. I nästa steg, aktiveras fosfaalkenen efter en nukleofil attack från en hydroxidbas och bildar *via* tautomerisering en sekundär fosfinoxid (SFO). Slutligen, låter man SFO-föreningen reagera med Aldehyd B för att bilda en alken med substituenter från båda aldehyder.[167]

Steg två i beskrivningen ovan, alltså aktiveringen av fosfaalkenen, utgör nyckelsteget i denna nya aldehydolefineringsmetod och bygger således en bro mellan den kemi som används för att beskriva låg-valenta fosfaalkener (P^{III}), och Horner-Wittig-typen av karbonylolefineringskemi som används för att beskriva hög-valenta fosfinoxider (P^{V}) (*Scheme 8.2*).


1st step: P=C formation
with 1st aldehyde
electron deficient
R
P=P
OEt
OEt
R1
EtO
R = Mes* or MesF
Chemistry of low-valent phosphorus
3rd step: Coupling
with 2nd aldehyde
electron deficient
via SPO and
electron rich via phosphinate
SPO
or
phos-
phinate
+ base,
R2
R1
H
or
R'O
Chemistry of high-valent phosphorus
2nd step: Activation of P=C
HO
Tautomerization
SPO
R'O
t-BuOOH
only for R = Mes*
phos-
phinate
Bridging P(III)- and P(V)-type chemistry

Scheme 8.2 Grafisk illustration av den reduktiva enkärlsreaktionen av två aldehyder vid användning av fosfanylfosfonatreagens.

En första studie av enkärlsreaktionens substratomfattning visade att reaktionen är begränsad till användandet av elektronfattiga aldehyder. Detta gäller både Aldehyd A och Aldehyd B, även om den senare har en något större substratomfattning och tillåter användandet av aromatiska, heterocykliska, alifatiska, samt vinyliska system – så länge de har elektronfattig karaktär.

För att bredda substratomfånget, modifierades reaktionssekvensen med målet att Aldehyd B även skulle kunna utgöras av aldehyder med elektronrik karaktär (Aldehyd A måste vara elektronfattig för att det första steget i reaktionen ska kunna ske). I den modifierade reaktionssekvensen används en alkoxidbas (istället för en hydroxid) som nukleofil i steg två. Detta resulterar i ett ökat antal syresubstituenter på fosfaalkenens fosforcentrumet, vilket leder till kortlivade fosfinatintermediat som, i jämförelse med SFO-föreningar (intermediaten som fås vid användning av hydroxidbaser), har högre reaktivitet gentemot elektronrika bensaldehyder. Den modifierade reaktionssekvensen möjliggör därmed tillverkningen av *trans*-stillbenmolekyler med så kallade ”push-pull-elektronegenskaper”.

I ett annat försök, lades modifieringens fokus på kopplingsreaktionens stereokemiska resultat. Med inspiration från den *Z*-stereoselektiva STILL-GENNARI-olefineringen,[143, 146] som använder sig av starkt elektrondragande substituenter på fosfonatreagensen, syntetiserades ett nytt $Mes^{F}P(H)P(O)(OEt)_2$ reagens med en elektronfattig skyddsgrupp, 2,4,6-$(CF_3)_3Ph$ (här noterad Mes^{F}). Användandet av detta nya reagens i en enkärlsreaktion (under samma förhållanden som i försöket med den skrymmande skyddsgruppen Mes*) resulterade mycket riktigt i en högre selektivitet för *Z*-isomeren.

Resultaten av ovanstående experiment visar att enkärlsreaktionen möjliggör övergångsmetallfri, reduktiv, homokoppling av aromatiska såväl som heterocykliska aldehyder till alkener, och allt detta med hög *Z*-stereoselektivitet. Inga tidigare rapporterade reaktioner har påvisat samma kombination av egenskaper och vår enkärlsreaktion är således den första av sitt slag.

I den sista delen av den här avhandlingen, presenteras ännu ett sätt att utöka reaktionens substratomfång. Denna strategi fokuserar på att minska det steriska skyddet av fosfaalkenintermediaten, eftersom sådana intermediat tenderar att vara väldigt reaktiva men samtidigt väldigt benägna att falla sönder.[80c, 81, 102b] För att få mer kunskap kring reaktiviteten samt stabiliteten hos den här typen av fosfaalkener, syntetiserades en serie olika trifenylfosfaalkener med hjälp av *fosfa*-PETERSON-reaktioner mellan PhP(Li)TMS och osubstituerade, elektronrika samt elektronfattiga, bensofenoner.

Genom analys av denna serie, fastställdes att dessa trifenylfosfaalkener deltar i kemiska jämvikter, i vilka de kan genomgå dimerisering och bilda motsvarande 1,2-difosfetaner och därifrån vidare polymeriseras till högre oligomerer och polymerer. Den slutgiltiga storleken på föreningen (dvs. om man får en monomer, oligomer eller polymer) beror på de elektroniska egenskaperna hos fenylgruppernas substituenter. Används elektronrika substituenter, skjuts jämvikten åt monomersidan och används elektronfattiga substituenter vill reaktionen helst genomgå di- eller oligomerisering. Nämnda processer sker ej omedelbart utan behöver längre reaktionstider för att uppnå jämvikt. Resultatet av denna undersökning tyder på att även trifenylfosfaalkener skulle kunna vara intermediatstrukturer i den typen av kopplingsreaktioner som beskrivs i denna avhandling.

Genom att gå vägen *via* trifenylfosfaalkenintermediat skulle man förmodligen kunna utöka reaktionens substratomfång till ett med ännu större variation av aldehyder och ketoner. Detta skulle i sin tur innebära ytterligare förbättringar av den reduktiva enkärlskarbonylkopplingsreaktionen.

Översatt av Sofie Ye

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