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Novel Organophosphorus Compounds for Materials and Organic Synthesis

KEYHAN ESFANDIARFARD



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Abstract

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This thesis is devoted to the development of new organophosphorus compounds for potential uses in material science and as reagents in Organic Chemistry. Organophosphorus compounds in a single molecule or organic electronics context are appealing as the phosphorous centers perturb the electronic properties of the π -conjugated systems while at the same time provide synthetic handles for subsequent synthetic modifications. As such, new synthetic methodology to such compounds and the exploration of new building blocks is of considerable interest. In a different study, novel organophosphorus compounds are synthesized and shown to promote a reaction in Organic Chemistry that has previously not been possible, *i.e.* the stereoselective reductive coupling of aldehydes to alkenes. Such developments enlarge the toolkit of reactions that are available to Organic Chemists, and may impact the synthetic routes to pharmaceuticals and other important commodity chemicals.

A general introduction of the key structural unit of this thesis, phosphalkenes, is given in the first chapter. The synthesis, reactivity, properties and applications of these P=C double bond containing compounds are highlighted. The Wittig reaction and its variations as well as the phosphorus analogues that produce phosphalkenes are outlined in detail.

The second chapter is dedicated to the synthesis of a precursor that is used for the preparation of novel π -conjugated, organophosphorus compounds. *C,C*-Dibromophosphalkenes are prepared and the halide substituents are used for the selective introduction of acetylene units. Besides the phosphalkenes, the successful syntheses of two new diphosphenes is presented, indicating a broad applicability of the precursors.

The third chapter is dedicated to the isolation of a metal-free phosphanylphosphonate that transforms aldehydes quantitatively to their corresponding *E*-phosphalkenes in a transition metal-free phospho-HWE (Horner-Wadsworth-Emmons) reaction. The reaction benefits from mild conditions, high *E*-stereoselectivity, and a broad substrate scope.

In the last chapter, a novel method for the reductive coupling of aldehydes to olefins is introduced. The reaction, which is a vast improvement over the McMurry coupling, allows for the selective synthesis of symmetrical and most importantly unsymmetrical *E*-alkenes. The phosphanylphosphonate mentioned above is the reagent that facilitates the coupling of the aldehydes via a phosphalkene intermediate. This one-pot reaction benefits from mild conditions, good conversions, and high *E*-stereoselectivity.

In summary, the thesis presents novel aspects of organophosphorus chemistry. These include the preparations and exploration of interesting precursors for the construction of π -conjugated organophosphorus compounds, and the use of organophosphorus reagents for unprecedented transformations in Organic Chemistry.

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To Mom and Dad

List of Papers

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

- I Esfandiartard K., Ott S., Orthaber A. (2015) Synthesis of 2,6-Dimesitylphenyl-*C,C*-dibromophosphaalkene. *Phosphorus, Sulfur, and Silicon*, 190, 816–820
- II Esfandiartard K., Orthaber A., Ott S. Synthesis of New Precursors for the Development of Low-coordinate Phosphorus Compounds. *Manuscript*
- III Shameem M. A., Esfandiartard K., Öberg E., Orthaber A., Ott S. (2016) Direct, Sequential, and Stereoselective Alkynylation of *C,C*-dibromophosphaalkenes. *Chem. Eur. J.*, 22, 10614-10619
- IV Esfandiartard K., Arkhypchuk A. I., Orthaber A., Ott S. (2016) Synthesis of the first metal-free phosphanylphosphonate and its use in the “phospha-Wittig-Horner” reaction. *Dalton Trans.*, 45, 2201-2207
- V Esfandiartard 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

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Contribution Report

Paper I. I performed all the synthetic work and measurements, except for the X-ray crystallography. I had major contributions in the design of the project, data analysis, and writing the manuscript.

Paper II. I performed all the synthesis and characterizations, except for the X-ray crystallography. I wrote the manuscript and had major contributions in the design of the project.

Paper III. I performed a part of the synthetic work and characterizations in order to extend the substrate scope and had contributions in writing parts of the manuscript.

Paper IV. I had major contributions in the design of the manuscript, except for the preliminary core idea of the project. I performed all the synthetic work and characterizations, except for the X-ray crystallography. I wrote the manuscript.

Paper V. I had major contributions in finding the mechanism and performed all the mechanistic experiments as well as doing half of the synthetic work and characterizations for the substrate scope. I contributed in the design of the project and writing the manuscript.

Contents

| | |
|---|----|
| 1. Background..... | 11 |
| 1.1. Phosphaalkenes | 11 |
| 1.1.1. Comparison between P=C and C=C Bonds..... | 11 |
| 1.1.2. Kinetic Stabilization of Phosphaalkenes..... | 12 |
| 1.1.3. Synthetic Routes for the Preparation of Phosphaalkenes | 13 |
| 1.1.4. Application of Phosphaalkenes..... | 15 |
| 1.2. Alkenes and Wittig Reaction..... | 16 |
| 1.2.1. Mechanism of Wittig Reaction | 17 |
| 1.2.2. Modifications of the Wittig Reaction | 18 |
| 1.2.3. Phosphorus Version of Wittig Reaction | 18 |
| 2. Dmp-Stabilized <i>C,C</i> -Dibromophosphaalkenes (Papers I, II, and III)..... | 21 |
| 2.1. <i>C,C</i> -Dihalophosphaalkenes | 21 |
| 2.2. Acetylenic Phosphaalkenes | 23 |
| 2.3. Design of New Precursors for Post-synthetic Purposes (Papers I and II)..... | 23 |
| 2.4. Synthesis and Isolation of the Dmp-Stabilized <i>C,C</i> -Dibromophosphaalkenes | 28 |
| 2.4.1. NMR Studies | 30 |
| 2.4.2. UV/Vis Studies | 32 |
| 2.4.3. Cyclic Voltammetry Studies..... | 32 |
| 2.5. “Acetylenic” Diphosphenes | 33 |
| 2.5.1. Related Diphosphenes in the Literature..... | 33 |
| 2.5.2. Synthesis of a New Dmp-Stabilized Diphosphene | 34 |
| 2.6. Sequential and Stereoselective Alkynylation of <i>C,C</i> -Dibromophosphaalkenes (Paper III) | 37 |
| 2.6.1. Development of a Stereoselective Procedure | 37 |
| 2.6.2. Application of the Method on the Dmp-Stabilized Phosphaalkenes..... | 39 |
| 2.7. Outlook..... | 41 |
| 3. Metal-free Phosphanylphosphonate and Transition Metal-free Phospha-HWE Reaction (Paper IV) | 42 |
| 3.1. Metal-coordinated Phosphanylphosphonates | 42 |
| 3.2. Isolation of the First Metal-free Phosphanylphosphonate..... | 44 |
| 3.3. Transition metal-free Phospha-HWE Reaction | 46 |

| | |
|---|----|
| 3.3.1 Substrate Scope..... | 47 |
| 3.3.2. <i>E/Z</i> Isomerization of Phosphaalkene Products | 48 |
| 3.3.3. Successful application of a Chromatography-free Purification Method on Phosphaalkenes | 50 |
| 3.4. Side-reactions of phospha-HWE Reaction..... | 51 |
| 3.5. Modified Reaction Conditions | 53 |
| 4. A Novel Entry into C=C Bond Formation via Organophosphorus Chemistry (Paper V) | 55 |
| 4.1. Synthetic Routes to 1,2-Disubstituted <i>E</i> -alkenes from Aldehydes.... | 55 |
| 4.2. Phosphaalkenes as Electrophiles | 57 |
| 4.3. Mechanistic Investigations on the Unexpected Side-reaction..... | 59 |
| 4.4. Shaping a One-pot Reaction..... | 63 |
| 4.5. Substrate Scope | 64 |
| 4.5.1. Homocoupling of Aldehydes to Symmetrical <i>E</i> -Alkenes..... | 65 |
| 4.5.2. Unprecedented Reductive Coupling of Two Different Aldehydes to Unsymmetrical <i>E</i> -alkenes..... | 66 |
| 4.6. Advantages over McMurry Reaction | 69 |
| 4.7. Limitations of the Reductive Aldehyde Coupling Method | 69 |
| 4.8. Outlook..... | 72 |
| 5. Concluding Remarks and Summary | 74 |
| Svensk sammanfattning | 76 |
| Acknowledgments..... | 78 |
| References..... | 80 |

Abbreviations

| | |
|-------|--|
| CAN | Cerium Ammonium Nitrate |
| CV | Cyclic Voltammetry |
| DBU | 1,5-Diazabicyclo[4.3.0]non-5-ene |
| DCM | Dichloromethane |
| Dmp | Dimesityphenyl |
| FBW | Fritsch-Buttenberg-Wiechell |
| HOMO | Highest Occupied Molecular Orbital |
| HWE | Horner-Wadsworth-Emmons |
| LDA | Lithium diisopropylamide |
| LUMO | Lowest Unoccupied Molecular Orbital |
| Mes | Mesityl, 2,4,6-trimethylphenyl |
| Mes* | Super mesityl, 2,4,6-tri- <i>tert</i> -butylphenyl |
| OLED | Organic Light Emitting Diode |
| SPO | Secondary Phosphine Oxide |
| TBAOH | Tetrabutylammonium hydroxide |
| THF | Tetrahydrofuran |
| TIPS | Triisopropylsilyl |
| TMS | Trimethylsilyl |
| Tol | Tolyl |
| Ts | Tosyl |

1. Background

Since the introduction of the classical double bond rule in late 40s, it was believed for decades that inter-element multiple bonding with a heavier main group element was not possible.^[1] However, progressive developments in main group chemistry, especially the rise of low-valent organophosphorus and organosilicon compounds, proved the classical double bond rule to be wrong. Since the first ever synthesis of phosphalkenes in 1976 by Becker,^[2] there have been numerous examples of low-coordinated main group compounds being synthesized for the first time. Notable amongst these are the synthesis of a diphosphene (P=P),^[3] silene (C=S),^[4] disilene (Si=Si),^[5] phosphalkyne (P≡C),^[6] silaphosphene (Si=P),^[7] dibismuthene (Bi=Bi),^[8] disilyne (Si≡Si),^[9] stibabismuthene (Sb=Bi),^[10] *etc.* The focus of this thesis is mainly on *phosphaalkenes* and their chemistry.

1.1. Phosphaalkenes

Phosphorus is sometimes referred to as the “carbon copy”^[11] or even “carbon photocopy”^[12] in the literature due to its surprising resemblance to carbon. Owing to such similarities, phosphalkenes can be seen as a “heavy olefin” since it shares many aspects with alkenes. This chapter provides a brief and general background about the features and properties that phosphalkenes possess.

1.1.1. Comparison between P=C and C=C Bonds

The P=C bond has many similarities to the C=C bond owing to related features of phosphorus and carbon atoms in terms of their electronegativities and ionization potentials (IP). The electronegativity of phosphorus is 2.19 on the Pauling scale compared to 2.55 for carbon. While the (2p-2p) π orbital of C=C is apolar, the (3p-2p) π of P=C is only slightly polarized. The first ionization potential of phosphorus is 1011.8 kJ/mol which is extremely close to that of the carbon atom (1086.5 kJ/mol). The two elements also have very close valence orbital energies according to Koopman's *theorem*. Valence orbital energies for 3p and 3s of phosphorus are -9.8 eV and -18.4 eV respectively which are very close to those of carbon (-10.7 eV for 2p and -19.4 eV for 2s).

The HOMO energy levels of ethylene and methylenephosphene ($\text{H}_2\text{C}=\text{PH}$) are very close to each other at -10.51 eV and -10.30 eV, respectively. The same trend is also observed for styrene ($\text{Ph}(\text{H})\text{C}=\text{CH}_2$) and *E*-1-phenylphosphaethene ($\text{Ph}(\text{H})\text{C}=\text{PH}$) where calculations show HOMO energy levels of -6.39 and -6.35 eV, respectively.^[13]

As a result, phosphalkenes exhibit similar behaviors in terms of chemical reactivity as alkenes. Along those lines, many standard olefin reactions such as hydrogenations, hydrohalogenations, polymerizations, epoxidations, *etc.* have also been reported for phosphalkenes.^[11]

Despite all of the similarities described above, phosphalkenes exhibit differences compared to alkenes. The energy level of the LUMO frontier orbital in a phosphalkene is considerably lower in energy compared to that of an alkene. This fact is actually the origin of many excellent properties that phosphalkenes exhibit. In section 1.1.4, some of these properties will be described in more detail.

1.1.2. Kinetic Stabilization of Phosphalkenes

Possessing a reactive $\text{P}=\text{C}$ bond in their backbone, phosphalkenes are prone to decomposition and unwanted polymerization. This is actually the main reason that isolation of phosphalkenes and other low-coordinated main group compounds was not thought possible until the classical double bond rule was proven invalid. Kinetic stabilization is the main strategy that allows phosphalkene isolation as it increases the energy level of the transition state towards decomposition while having minimal influence on the enthalpy. Such stability is achieved by the installation of sterically bulky groups on either one or both termini of the $\text{P}=\text{C}$ bond.

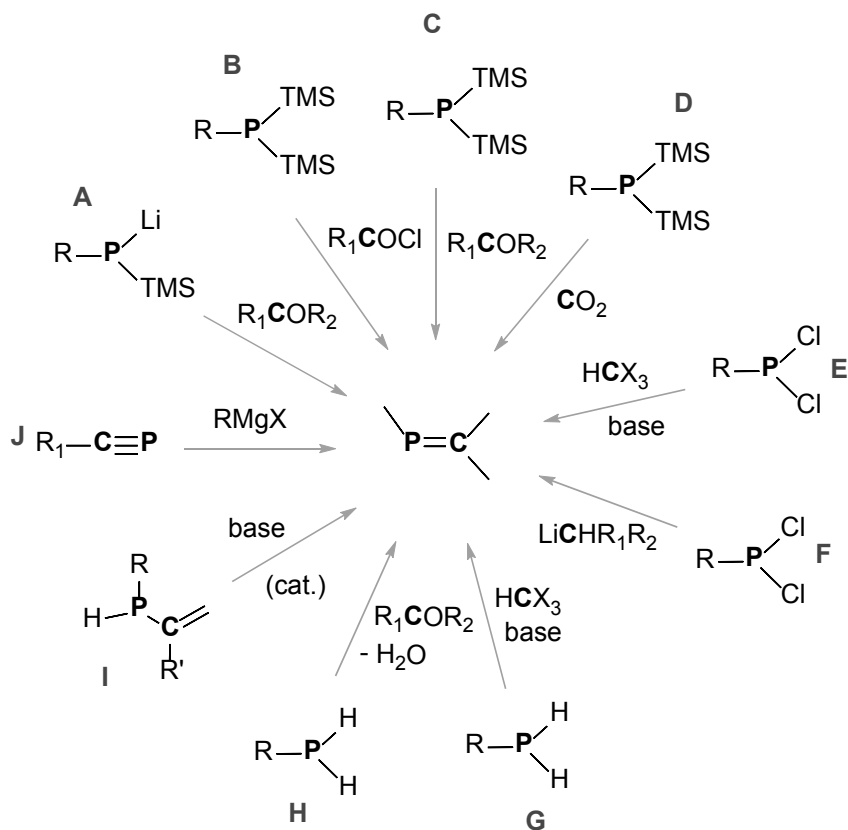
Many examples of protecting groups used for the stabilization of phosphalkenes have been reported throughout the past decades. Some are incorporated on the molecule solely for the purpose of steric protection while others have electronic effects on the phosphalkene compound as well. Stabilization of inter-element linkages via steric or electronic effects is thoroughly discussed in a review by Yoshifuji^[14] which is recommended for further reading.

Among the many examples of protecting groups for phosphalkenes, 2,4,6-tri-*t*-butylphenyl known as Mes^* or “super mesityl”, is probably the most established in the category. Its steric shape and spatial bulkiness as well as the straightforward synthesis of the Mes^*Br starting material,^[15] are the main reasons for the popularity of the Mes^* group. Another common stabilizing group is 2,6-dimesitylphenyl, known as Dmp, which benefits from the steric protection of the two mesityl “wings” on its central phenyl moiety. Dmp and Mes^* are the main stabilizing groups that were used in this thesis work.

It is important to note that phosphalkenes can be stabilized also through coordination of a metal fragment to their P-lone pair. This type of stabilization, which is not kinetic, is utilized in metal-coordinated phospho-Wittig reactions and will be discussed more in detail in this thesis.

1.1.3. Synthetic Routes for the Preparation of Phosphalkenes

Many procedures for the preparation of phosphalkenes have been developed during the past decades. A selection of these synthetic pathways is depicted in Scheme 1.

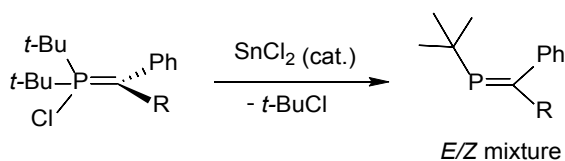


Scheme 1. Synthetic routes to phosphalkenes

Phosphalkenes can be prepared through the reaction of mono-silylated phosphines with carbonyl compounds (A).^[16] Also, the reaction of di-silylated phosphines with carbonyl compounds such as acyl chlorides (B),^[17] aldehydes, ketones, or amides (C),^[18] and even carbon monoxide (D)^[19] gives the corresponding phosphalkene products via a phospho-Peterson

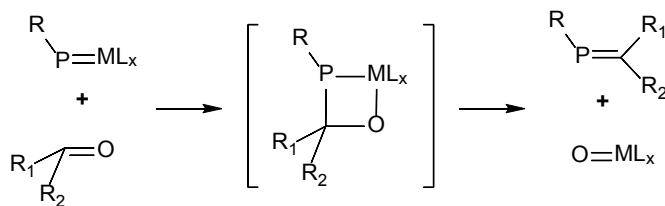
mechanism. Dichlorophosphines are among the most common starting materials for the preparation of phosphalkenes. Their reaction with a haloform and LDA gives the corresponding dihalophosphaalkenes (**E**).^[20] In general, a lithiated carbon species (LiCHR_1R_2) can react with dichlorophosphines and lead to the formation of P-C single bonds. Addition of a base leads to a subsequent 1,2-elimination and gives the corresponding $\text{R-P}=\text{CR}_1\text{R}_2$ phosphalkene products (**F**).^[21] Primary phosphines can also be used as starting materials and reacted with haloforms or dihalomethanes (**G**)^[22] or carbonyl compounds in a condensation reaction (**H**) in order to afford the corresponding phosphalkenes. Secondary vinylphosphines which are themselves prepared from dichlorophosphines can undergo a base-catalyzed reaction and yield the phosphalkene products (**I**).^[23] Finally, the reaction of phosphalkynes with RMgX Grignard reagents can also afford the phosphalkene products through the attack of the R group at the phosphorus center to transform the $\text{P}\equiv\text{C}$ bond into a $\text{P}=\text{C}$ bond (**J**).^[24] There have even been interesting examples of transition metal (usually Ru) complexes reacting with phosphalkynes to afford the corresponding phosphalkene complexes.^[25]

In addition to the synthetic methods described above, one can also mention an interesting, but unconventional method that was reported by Grützmacher and colleagues,^[26] where catalytic SnCl_2 eliminates *t*-BuCl from a P-chlorinated phosphorus ylide in order to give the corresponding phosphalkenes (Scheme 2).



Scheme 2. An unconventional synthetic route to phosphalkenes

Reaction of phosphinidene complexes with carbonyl compounds can be added to this category as well (Scheme 3).^[27]



Scheme 3. Synthesis of phosphalkenes using phosphinidene complexes

One could imagine this reaction as a phosphorus version of the Tebbe olefination. In this way, phosphinidene complexes can be considered as the active phospha-Tebbe reagent that transforms the carbonyl compounds to their corresponding phosphaalkene products (Scheme 3).

1.1.4. Application of Phosphaalkenes

As mentioned earlier, phosphorus and carbon are surprisingly similar in many aspects such as electronegativity and valence orbital energy. At the same time, they are also quite different. For example, the presence of a lone pair on phosphorus as well as its different oxidation states are traits that are absent in the carbon atom. As a result, phosphaalkenes can be exploited in areas such as electronics and polymer chemistry similar to olefins, but can also be applied in other fields like coordination chemistry in a way that olefins cannot.

Polymerization

Phosphaalkenes are interesting building blocks that can be used as monomers for the fabrication of polymers.^[28] Mainly introduced by Gates and Protasiewicz, various phospha-PPVs featuring P=C bonds in the main chain of polymers have been reported (Figure 1).^[29]

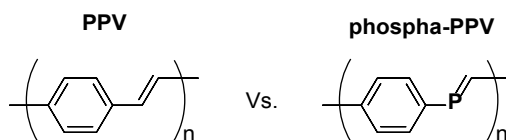


Figure 1. PPV and its phosphorus analogue

These polymers have been prepared via different strategies such as phospha-Wittig reaction^[30] and anionic initiation.^[31]

Organic Electronics

Incorporation of a heteroatom such as phosphorus into the π -conjugated frameworks of organic molecules has proven valuable to alter the properties of the materials. In this way, the compound's band gap can be tuned and other opto-electronic features can be added to the system.^[32] Due to their smaller HOMO-LUMO gap compared to that of the olefins (Figure 2), phosphaalkenes are potentially invaluable building blocks for the construction of larger π -conjugated architectures and ultimately electronic devices such as semi-conductors, LEDs, photovoltaics and the like.

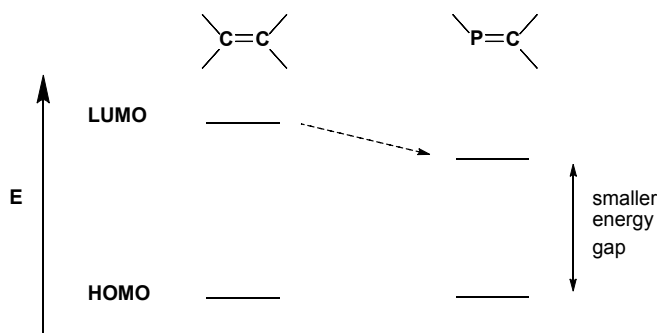


Figure 2. Comparison of the HOMO-LUMO gaps in alkenes and phosphalkenes

Coordination Chemistry

Phosphalkenes have found growing attention and application as ligands in coordination chemistry.^[33] They can have two different bonding modes: η^1 and η^2 (Figure 3).

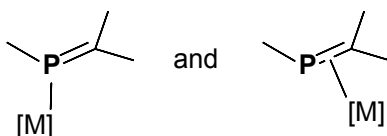


Figure 3. Most common bonding modes of a phosphalkene. *Left:* η^1 , *Right:* η^2

The η^2 bonding mode of phosphalkenes is similar to that of alkenes. Owing to the presence of the lone pair on the phosphorus center, phosphalkenes function similarly to classical phosphine ligands in their η^1 bonding mode. Phosphalkenes featured as monodentate or chelating (including pincer) ligands in their corresponding complexes.^[34] Phosphalkene complexes such as their monogold or digold structures have found application in catalysis.^[35] Finally, phosphalkenes were recently reported as novel ligands for the stabilization of gold nanoparticles (AuNPs).^[36]

1.2. Alkenes and Wittig Reaction

Alkenes are one of the most essential feedstock materials with broad industrial uses. Numerous synthetic methods exist for making alkenes, and many of these have found their way to industrial applications. Wittig olefination is one of the most established methods for making alkenes. This reaction was first introduced^[37] by Georg Wittig and Georg Geissler in 1953 and won the Noble Prize in Chemistry for Wittig in 1979.

1.2.1. Mechanism of Wittig Reaction

Due to its great importance, there have been a lot of studies and reviews about the Wittig reaction and its mechanism.^[38] In the Wittig reaction, aldehydes or ketones react with a phosphonium ylide to give the alkene products. Bearing a nucleophilic carbon, the phosphonium ylide is the active species in the reaction, although it can also be drawn in its ylene resonance form (Figure 4).

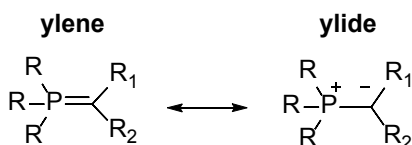
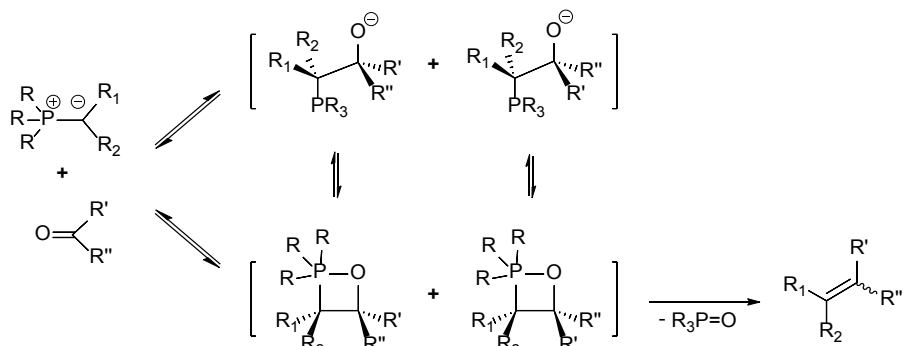


Figure 4. Phosphonium ylide and its ylene resonance form

The phosphonium ylide attacks the carbonyl compound to give a betaine intermediate which then forms a 4-membered oxaphosphetane intermediate. Collapse of the latter gives the alkene product and a phosphine oxide by-product.



Scheme 4. The mechanism of Wittig reaction

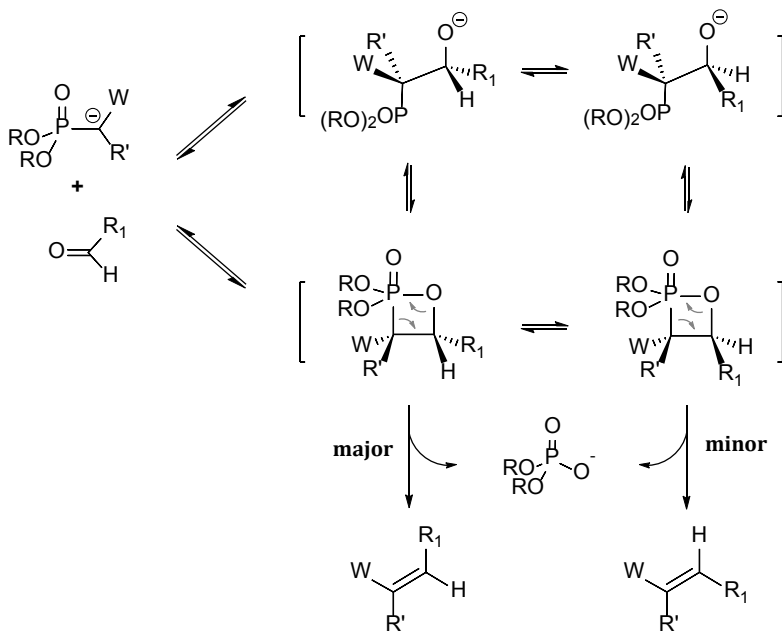
In the classical Wittig reaction, R_1 and R_2 on the α -carbon of the phosphonium ylide are usually alkyl groups. Such ylides are non-stabilized and very reactive as they react with both aldehydes and ketones to give *Z*-alkenes stereoselectively. On the other hand, stabilized phosphonium ylides are less reactive and react mainly with aldehydes to give *E*-alkene products. R_1 and R_2 are usually anion stabilizing groups in these cases. Thus, the stereochemical outcome of the reaction is defined by the type of phosphonium ylide used. Non-stabilized ylides give *syn* oxaphosphetane intermediates which form the *Z*-alkene products while stabilized ylides give *anti* oxaphosphetanes which eventually collapse to the *E*-alkene products (Scheme 4).

1.2.2. Modifications of the Wittig Reaction

Since the introduction of the Wittig reaction, some major modifications to the reaction have been developed by different research groups.^[39] One of the most important modifications of the Wittig reaction is Horner-Wadsworth-Emmons (HWE) reaction which is discussed herein.

Horner-Wadsworth-Emmons (HWE) Reaction

The HWE reaction that utilizes stabilized phosphonate carbanion reagents is one of the most widely used modification of the Wittig reaction.^[40] These carbanions are stabilized by electron withdrawing groups such as esters or nitriles and are generally more nucleophilic and basic than their phosphonium ylide congeners. As a result, the HWE reaction is applicable to both aldehydes and ketones. It gives *E*-alkene products selectively along with a phosphate by-product that is readily removable by aqueous work-up. The mechanism of HWE reaction is similar to that of Wittig reaction (Scheme 5).



Scheme 5. Mechanism of HWE reaction; W = CO₂R, CN, aryl, vinyl, *etc.*

1.2.3. Phosphorus Version of Wittig Reaction

In the phosphorus version of Wittig reaction, a *phosphorus ylide* reacts with a carbonyl compound and produces the phosphalkene products (Figure 5).

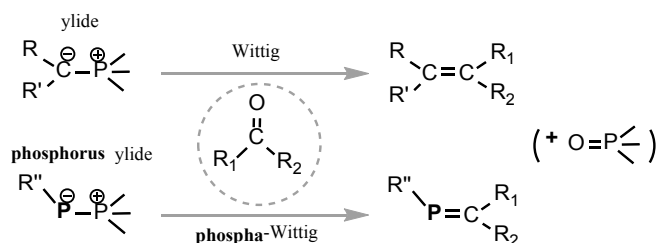


Figure 5. Wittig reaction and its phosphorus analogue

There are two phosphorus versions of Wittig reaction in the literature which are classified and depicted in Figure 6.

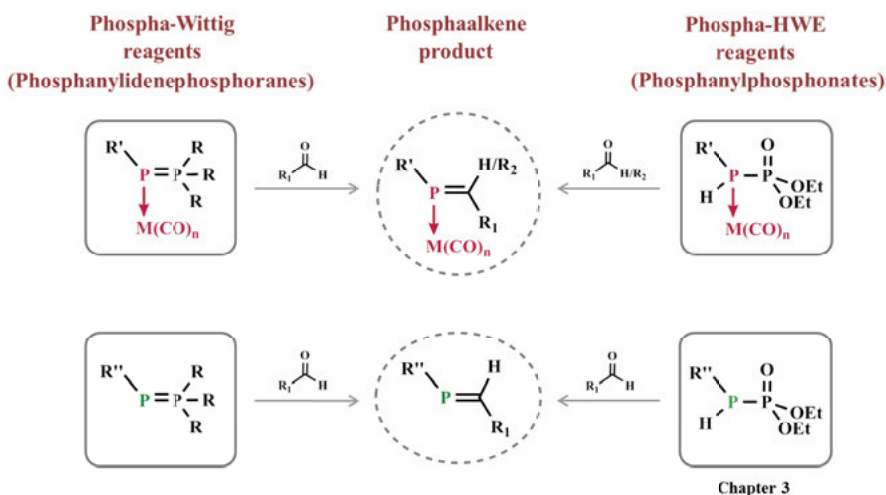


Figure 6. Phosphorus analogues of the Wittig-related reactions. *Left:* metal-coordinated and transition metal-free phospho-Wittig reactions. *Right:* metal-coordinated phospho-HWE and its transition metal-free version. R = Me, Ph, *etc.*; R' = Me, Ph, alkyl, *etc.*; R'' = bulky stabilizing groups such as Mes* or Dmp

Phospha-Wittig:

The first example of a phospho-Wittig reaction was reported by Protasiewicz *et al* in 1998 where aldehydes (but not ketones) were converted to the corresponding phosphoalkene products by a phosphanylidene phosphorane reagent.^[41] A metal-coordinated version of this reaction was also reported in 2011 by Mathey *et al.*^[42]

Phospha-HWE reaction:

A phosphorus analogue of HWE reaction was first introduced in 1988 by Mathey and co-workers.^[43] In their phospha-HWE reaction, phosphaalkene products were complexed to a transition metal (W, Mo, or Fe) in order to make them stable and isolable. Such metal-coordination was directly transferred from a metal-complexed phosphanylphosphonate reagent to the phosphaalkene product. Prior to this thesis, there had been no reports of a transition metal-free phospha-HWE reaction where uncomplexed phosphaalkenes are obtained as products (see Chapter 3).

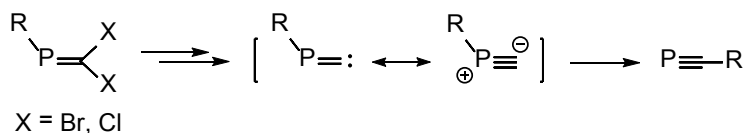
2. Dmp-Stabilized C,C-Dibromophosphaalkenes (Papers I, II, and III)

In papers I and II, the synthesis and isolation of a series of low-valent phosphorus compounds is described. The compounds are kinetically stabilized by a bulky Dmp (= dimesitylphenyl) group and are valuable precursors for post-synthetic purposes. In paper III, a new methodology for the direct and sequential alkynylation of phosphoalkenes is described. In addition to the Dmp-stabilized phosphoalkenes, the alkynylation is also applied to Mes*-stabilized phosphoalkenes, and the results and applicability of the two different phosphoalkenes to the procedures is discussed.

2.1. C,C-Dihalophosphaalkenes

Bearing two halo groups on their P=C<, C,C-dihalophosphaalkenes are invaluable compounds for post-synthetic manipulations. The reactivity of the P=C bond in C,C-dihalophosphaalkenes follows that of phosphoalkenes in general. However, the halogens on the P=C< provide extra reactive sites to the phosphoalkene and the majority of the post-synthetic manipulations in fact stem from the presence of these halogens on the molecule. Dibromo- and dichloro-phosphaalkenes are the most widely utilized C,C-dihalophosphaalkenes while diiodophosphaalkenes are rarely used and difluorophosphaalkenes have had no reported post-synthetic use.

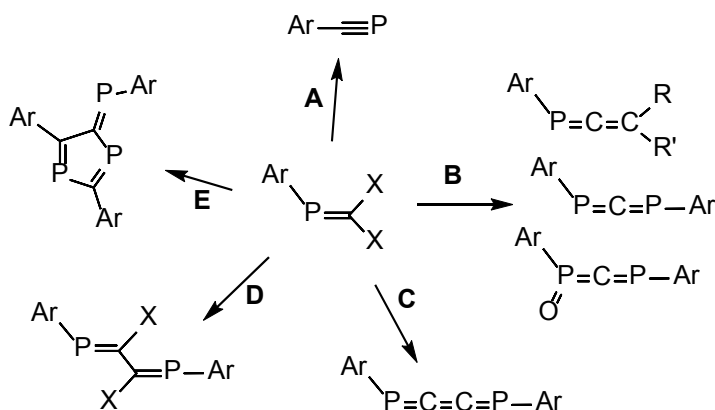
Since their first synthesis in 1985, there has been numerous examples employing C,C-dihalophosphaalkenes as precursors.^[44] One of the most common approaches for making phosphoalkynes is via the Fritsch-Buttenberg-Wiechell (FBW) rearrangement of intermediates that are derived from C,C-dihalophosphaalkenes (Scheme 6).



Scheme 6. Conversion of the C,C-dihalophosphaalkene to phosphoalkyne product in a phospha-FBW rearrangement through 1,2-migration of the R group

This reaction can occur through lithiation-promoted procedures^[45] as well as transition metal-mediated^[46] or -catalyzed^[47] methods.

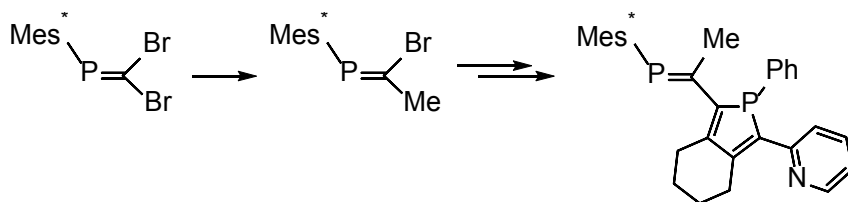
In addition to the preparation of phosphalkynes (**A**), *C,C*-dihalophosphaalkenes are the starting material for the synthesis of many exotic low-valent phosphorus compounds including phosphallenes (**B**),^[48] phosphacumulenes (**C**),^[49] phosphabutadienes (**D**),^[49] and phosphafulvenes (**E**) (Scheme 7).^[50]



Scheme 7. Synthesis of interesting but less common low-valent phosphorus compounds from *C,C*-dihalophosphaalkene Ar-P=CX_2 (Ar = usually Mes^* , X = Br, Cl)

Moreover, *C,C*-dihalophosphaalkenes have been used for the preparation of more elaborate π -conjugated systems containing other main group elements such as Si, Ge, As, and Sb.^[51] For example, one can include the synthesis of the first germa- and arsa-phosphaallene in this category.^[52]

C,C-Dihalophosphaalkenes are excellent starting materials for the construction of sophisticated π -conjugated architectures that contain P=C bonds in their backbone.^[51b, 53] Phosphole-phosphaalkenes which possess a P=C moiety and a phosphole ring in the same molecule are interesting examples of such structures (Scheme 8).^[54]



Scheme 8. Synthesis of a phosphole-phosphaalkene from $\text{Mes}^*\text{P=CBr}_2$

2.2. Acetylenic Phosphaalkenes

Acetylenic bridges are versatile units for the construction of larger π -conjugated, acetylenic structures, and have been applied in single molecular electronics due to their conductive and opto-electronic features.^[55] On the other hand, the inclusion of a heteroatom such as phosphorus into an all-carbon π -conjugated scaffold can alter electronic properties such as the HOMO-LUMO gaps significantly. Moreover, incorporation of a phosphorus atom into π -conjugated architectures can add polarizability and coordination site to such systems.

Appel *et al.*^[56] and our research group^[21e, 32, 53a, 57] have developed various phosphaalkenes with acetylenic substitutions on the P=C bond (Figure 7). These phosphaalkenes include *P*-monoacetylenic (**I**), *C*-monoacetylenic (**II**) and *C,C*-diacetylenic (**III**) structures. The synthesis of a *P,C*-diacetylenic (**IV**) or *P,C,C*-triacetylenic (**V**) phosphaalkene however has consistently proven to be an elusive challenge. The problem is that a single acetylenic substituent on the P-atom is insufficient to stabilize the molecule. This instability may be compensated by the presence of bulky stabilizing groups on the C-terminus of the P=C bond as in **I**.

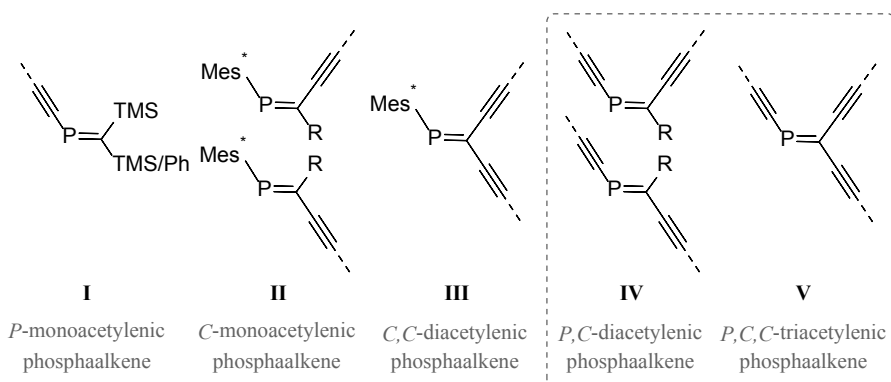


Figure 7. All possible forms of acetylenic phosphaalkenes. The phosphaalkenes in the dashed box are synthetically elusive.

2.3. Design of New Precursors for Post-synthetic Purposes (Papers I and II)

To date, there has only been one example of *P*-acetylenic phosphaalkenes in the literature. The structure of that molecule is somewhat constrained as the C-center of the P=C moiety can only bear TMS and/or Ph groups in order for the compound to be isolable (Figure 7, **I**). Such structural restriction has made the isolation of *P,C*-di- and *P,C,C*-tri-acetylenic phosphaalkenes unreachable.

Phosphaalkenes reported in the literature are designed and synthesized in a way such that the P-atom always bears a bulky group and a diverse range of substituents can be bound to the C-atom of the P=C bond. The group attached to the phosphorus plays a key role for the stabilization of the phosphaalkene in order to circumvent its decomposition or polymerization. On the other hand, the C-atom of the P=C bond can carry substituents as simple as two hydrogens or as sophisticated as long conjugated groups or bridges. To the best of our knowledge, there have only been one report thus far for P-protecting groups with further functionalization sites which include vinylic substituents at the *para* position of the Dmp group.^[29b]

Inspired by these reports, we decided to design a new phenyl-based protecting group with an acetylenic moiety in *para*-position relative to the P-center (Figure 8). With suitable bulky groups in the *ortho*-positions, phosphaalkenes that carry this protection group would enjoy kinetic stability along with an extendable acetylenic substituent. Since two *ortho* *t*-Bu groups on the phenyl group generally provide the highest stability for low-valent organophosphorus molecules, the best candidate for our purpose would be a Mes* -like group with an acetylenic substituent at its *para* position.

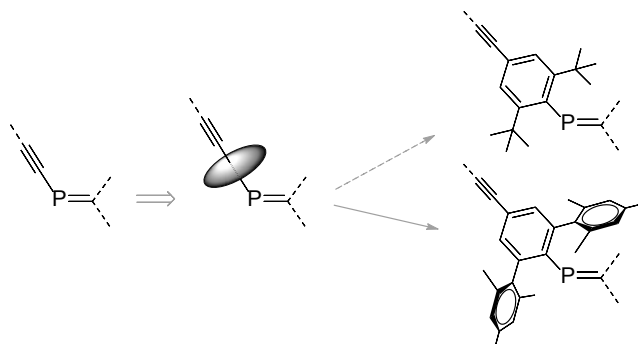
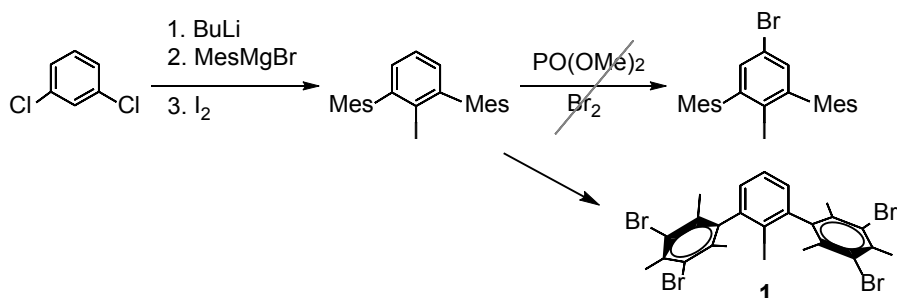


Figure 8. Design of the ‘P-acetylenic’ phosphaalkenes. A *para*-acetylenic Dmp group was chosen to provide stability for the phosphaalkene as well as an acetylenic extension on the “phosphorus side”.

Yoshifuji *et al* reported the direct bromination of 1-bromo-2,6-di-*t*-butylbenzene which afforded the *para*-brominated species, 1,4-dibromo-2,6-di-*t*-butylbenzene, in 63% yields. 1,4-dibromo-2,6-di-*t*-butylbenzene would be the perfect precursor for our purpose as a simple Sonogashira coupling could give the *para*-acetylenic compound. However, we decided against pursuing this synthesis as the pathway to reach 1-bromo-2,6-di-*t*-butylbenzene is long and tedious.^[20b]

A *para*-acetylenic Dmp was our next candidate as it seemed to be more readily available. Dmp-I was prepared in a reaction between the Grignard reagent MesMgBr and 1,3-dichlorobenzene, followed by quenching with I₂ as reported.^[58] We were curious to determine if a direct bromination was

applicable on Dmp-I as this would be the fastest path to the desired *para*-substituted compound. Unfortunately, the reaction outcome was different and a tetra-bromination took place instead, leaving the mesityl rings fully brominated and the central phenyl ring unaffected (Scheme 9).



Scheme 9. Attempts to execute a direct bromination at the *para* position of the Dmp moiety failed and a neat tetrabromination of the mesityl wings occurred instead.

The tetrabromination reaction occurred very neatly as the TLC analysis showed only one single spot, indicating the full conversion of Dmp-I to the tetrabrominated compound **1**. Single crystals of the compound suitable for X-ray crystallography were obtained by slow evaporation of a hexane solution (Figure 9).

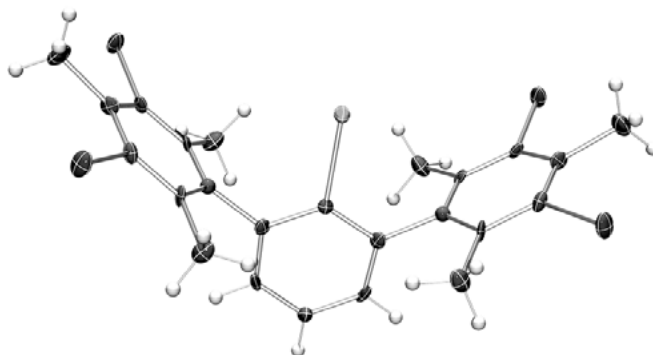
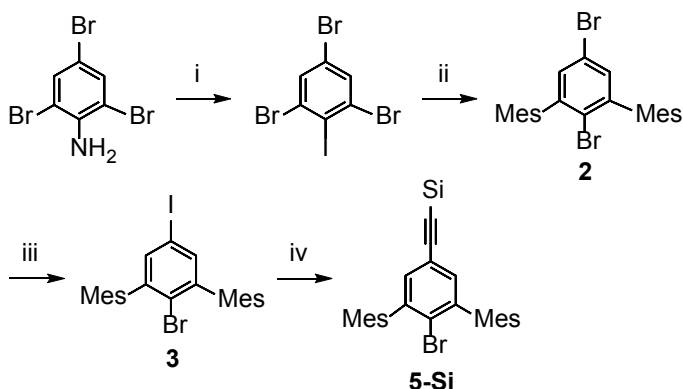


Figure 9. ORTEP representation of tetrabrominated compound **1**.

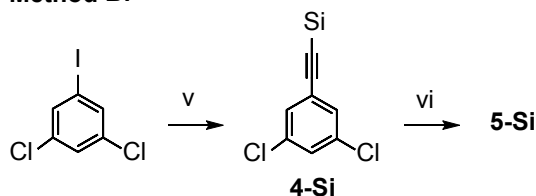
Considering the problems in functionalizing Dmp-I, an advantageous strategy would be to start the reaction sequence with a compound that already contains a halide at its *para* position. Two different methods to make the desired acetylenic substituted compound via this strategy are presented. Both methods afford compound **5-Si** successfully, although the second method is preferred since it is more convenient and has fewer steps (Scheme 10). **Method A:** a diazotization reaction of the commercially available 2,4,6-

tribromoaniline initiates the sequence. A subsequent Grignard reaction results in the incorporation of the mesityl groups and the formation of compound **2** that is subjected to a halogen exchange to give compound **3**.^[59] A selective Sonogashira coupling is then possible at this stage as the iodo-substituent is more reactive towards the coupling as well as being sterically more accessible.

Method A:



Method B:



Scheme 10. Synthesis of **5-Si** via: **Method A:** (i) HCl, 0 °C, NaNO₂, H₂O, 30 min, KI, 1 h, 88%. (ii) MesMgBr, THF, reflux, o.n., 0 °C, Br₂, r.t., 2 h, 28%. (iii) -78 °C, BuLi, 1 h, I₂, r.t., 75%. (iv) PdCl₂(PPh₃)₂, CuI, NEt₃, (Si)-acetylene, THF, 50 °C, 1 h, 98% (Si = TIPS). **Method B:** (v) PdCl₂(PPh₃)₂, CuI, NEt₃, (Si)-acetylene, THF, 0 °C, 1 h, 99%. (vi) -78 °C, BuLi, THF, MesMgBr, r.t., 16 h, reflux, 4 h, 0 °C, Br₂, 3 h. **5-TMS:** 35%; **5-TIPS:** 43%

Method B: Sonogashira coupling of 1,3-dichloro-5-iodobenzene initiates the sequence. The iodo-substituent is selectively replaced by the acetylenic moiety while leaving the two chloro-substituents intact. Grignard reaction of resultant **4-Si** with MesMgBr affords the desired **5-Si**.

Single crystals of the TIPS-ethynyl-protected compound **5-TIPS** could be obtained by slow evaporation of an *n*-hexane solution, and its crystal structure is shown in Figure 10.

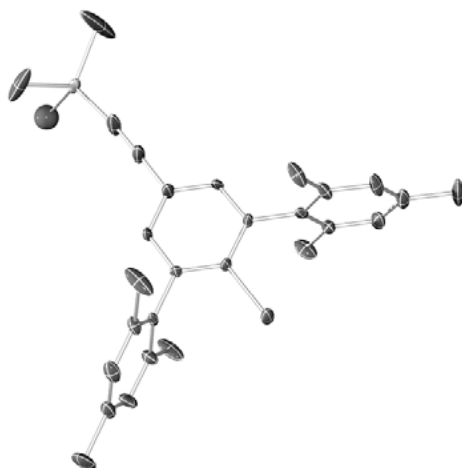
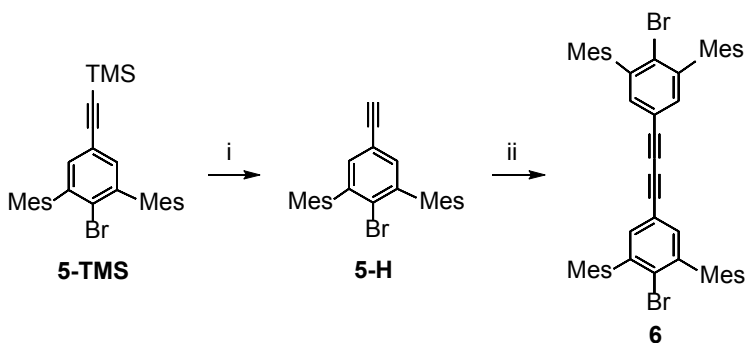


Figure 10. ORTEP plot of compound **5-TIPS**. Hydrogen atoms are omitted for clarity.

A useful feature of precursor **5-Si** is its potential to be further functionalized at its acetylenic terminus. A simple Si-deprotection provides a reactive site which allows such manipulations on the molecule. For example, deprotection of **5-TMS** gives acetylene **5-H** which can then give the homo-coupling product **6** (Scheme 11). Compound **6** is a valuable precursor itself as it can be used to make a series of “dimeric” low-valent products or even polymeric targets.



Scheme 11. Synthesis of the dimeric precursor **6** through the homocoupling reaction of **5-H**. i) Si = TMS; K_2CO_3 , THF/MeOH, 97%. ii) Piperidine, $Cu(OAc)_2 \cdot H_2O$, THF, 35 °C, 91%.

Almost all Dmp-containing compounds that were described above share one advantageous trait during their purification. The compounds show surprisingly poor solubility in acetone, making their purification extremely simple. Generally, after following the reaction progress by TLC until its completion and subsequent removal of the volatiles, one can simply wash off all the impurities with acetone to obtain the pure Dmp-containing compounds.

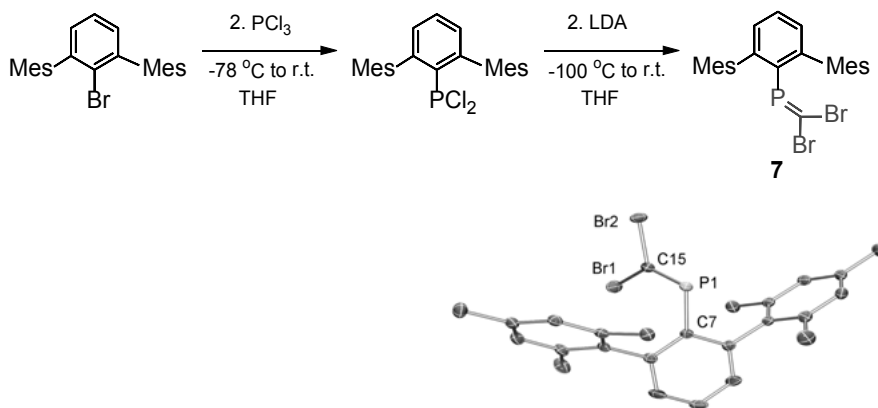
2.4. Synthesis and Isolation of the Dmp-Stabilized *C,C*-Dibromophosphaalkenes

Having synthesized compounds **5-Si** and **6**, the synthesis of their corresponding *C,C*-dibromophosphaalkenes was targeted. Such phosphoalkenes can potentially be used as precursors for the preparation of more elaborate π -conjugated structures such as acetylenic phosphoalkenes.

DmpP=CBr₂

Our series of *C,C*-dibromophosphaalkenes begins with the simplest Dmp-containing *C,C*-dibromophosphaalkene. A Grignard reaction of 1,3-dichlorobenzene with MesMgBr was conducted to obtain Dmp-Br after quenching the reaction with bromine. Lithiation followed by the addition of PCl₃ affords the dichlorophosphine Dmp-PCl₂. The reaction with bromoform and two equivalents of LDA results in the quantitative conversion of Dmp-PCl₂ to the corresponding *C,C*-dibromophosphaalkene **7** (Scheme 12) which is isolated in moderate yields (40-50%).

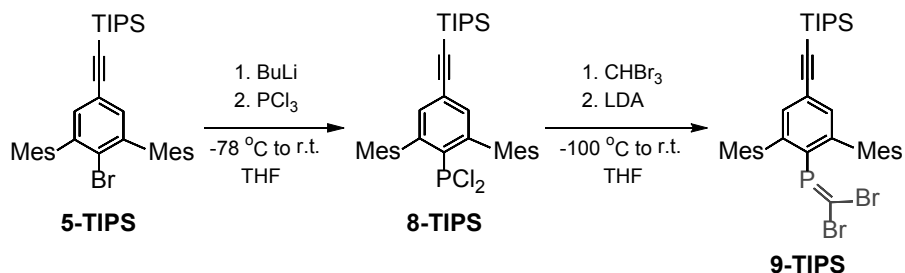
It is noteworthy that the lithiation was never complete when the sequence was started with Dmp-I. The desired *C,C*-dibromophosphaalkene consequently contained co-crystallized Dmp-I as an impurity. Simply changing from Dmp-I to Dmp-Br solved this problem and afforded the favored phosphoalkene free of any impurities. White crystals of the product (**7**) suitable for X-ray crystallography were obtained from a saturated solution of *n*-hexane (Scheme 12).



Scheme 12. Synthesis of DmpP=CBr₂ **7** from Dmp-Br through the formation of Dmp-PCl₂. Starting from Dmp-I does not provide a neat lithiation, resulting in difficulties in purification. The product was isolated by recrystallization in moderate yields (40-50%).

TIPS(CC)DmpP=CBr₂

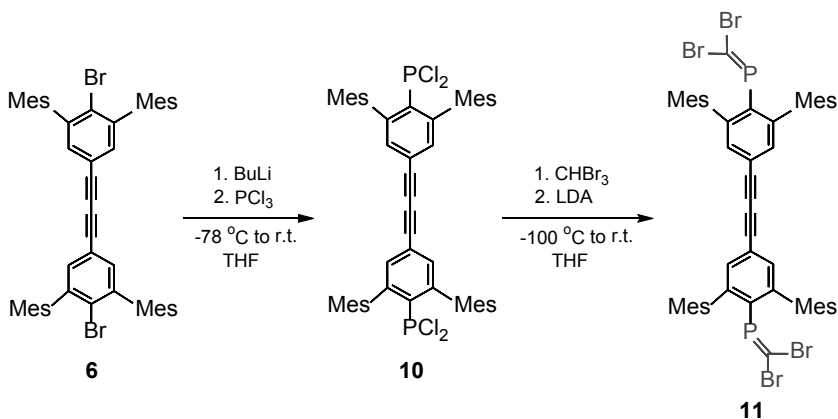
Following the same procedure, lithiation of the precursor **5-TIPS** and subsequently quenching with PCl₃ gave dichlorophosphine **8-TIPS**. After removing the volatiles, the residue was used for the next step without further purification. Reaction of dichlorophosphine **8-TIPS** with bromoform and two equivalents of LDA afforded pure phosphalkene **9-TIPS** in 42% (Scheme 13).



Scheme 13. Synthesis of dibromophosphaalkene **9-TIPS** from precursor **5-TIPS**. The product was isolated by recrystallization in 42% yield.

Br₂C=PDmp(C)₄DmpP=CBr₂

The next compound prepared was a dimeric dibromophosphaalkene. Double lithiation followed by reaction with electrophilic PCl₃ gave bis-dichlorophosphine **10** selectively with only traces of the mono-substituted compound detected. Finally, reaction of **10** with bromoform and 4 equivalents of LDA afforded bis-phosphaalkene **11** (Scheme 14).



Scheme 14. Synthesis of the dimeric phosphalkene **11** from dimer **6**; **11**: 51%

Recrystallization from a saturated solution of DCM in the freezer provided white crystals of diphosphaalkene **11** suitable for X-ray crystallography

(Figure 11). Recrystallization from a saturated solution of *n*-hexane was also successful and afforded the pure product.

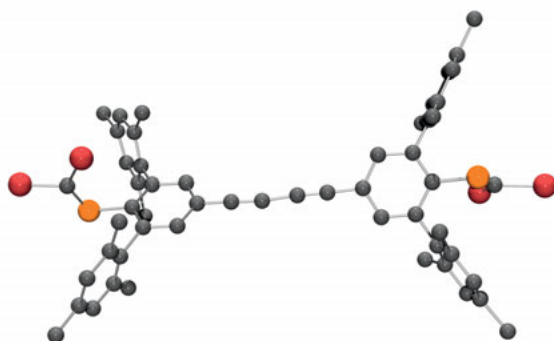


Figure 11. ORTEP representation of the dimeric phosphalkene **11**. Hydrogen atoms are omitted for clarity.

All the synthesized dibromophosphaalkenes **7**, **9-TIPS**, and **11** were found to be stable towards moisture or heat only for a short period of time (1-2 hours). However, aqueous work-up and subsequent manipulations were tolerated as long as the phosphalkenes were not exposed to moisture or to ambient temperature for a longer period of time. Isolated phosphalkenes could be stored under inert gas in the freezer for several months without any sign of decomposition.

2.4.1. NMR Studies

All transformations described above were monitored by ^{31}P NMR spectroscopy. The signal at 162 confirmed the formation of DmpPCl_2 while dichlorophosphines **8** and **10** both resonated at 159 ppm. Full consumption of the dichlorophosphines gave rise to signals at 273, 269, and 267 ppm which correspond to dihalophosphaalkenes **7**, **9-TIPS**, and **11**, respectively.

The ^1H NMR spectra of **7**, **9-TIPS**, and **11** showed a broadening of signals both in the aliphatic and aromatic regions at room temperature. Such spectroscopic behavior stems from a rotational hindrance in these molecules as the mesityl rings of the Dmp group clash sterically with the $-\text{P}=\text{CBr}_2$ moiety. As a result, two broad signals appear which are assigned to the *ortho*-methyl groups and *meta*-protons of the mesityl rings.

Representative VT- ^1H NMR spectra of **7** are depicted in Figure 12. Two sets of singlets resonate at 2.0 and 2.3 ppm as well as at 6.9 and 7.0 ppm at reduced temperatures. Heating up the sample leads to coalescence and broadening of signals at room temperature, and sharpening of the signals at higher temperatures. Similar spectroscopic behavior was also observed in the

^{13}C NMR spectra of the compounds with two distinct broad signals resonating at 21 ppm and 129 ppm in the aliphatic and aromatic regions, respectively.

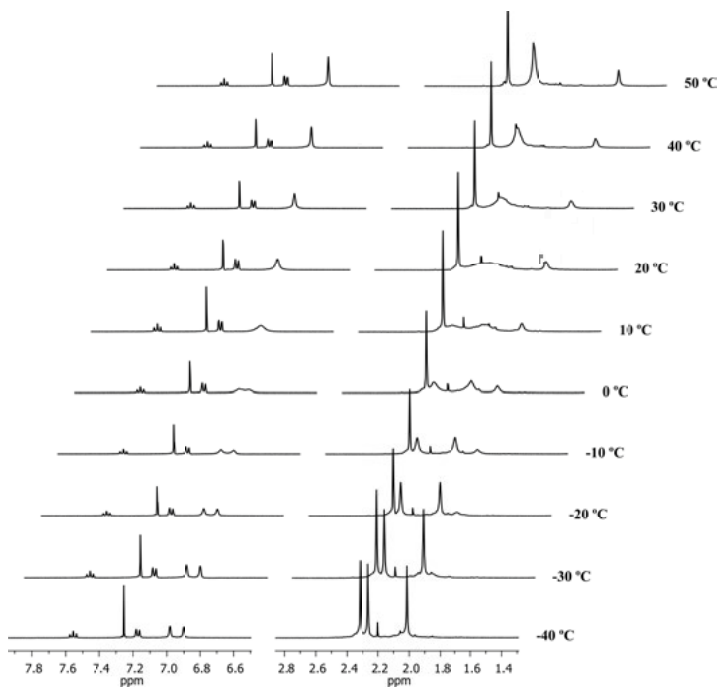


Figure 12. VT- ^1H NMR spectra of dibromophosphaalkene **7** (CDCl_3). Coalescence of the signals by temperature increase is observable in the aliphatic and aromatic regions.

It is worth noting that *C,C*-dichlorophosphaalkenes do not show such broadening in their NMR spectra. We therefore assume that the size of the halogen and therefore $\text{P}=\text{CX}_2$ ($\text{X} = \text{Br}, \text{Cl}$) moiety has a direct impact on the rotational hindrance of the molecule (Figure 13).

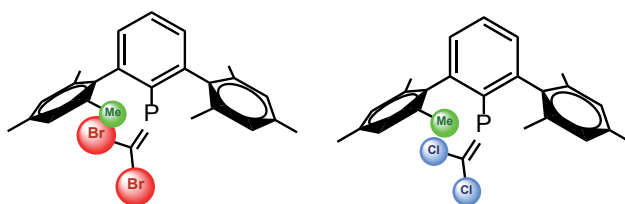


Figure 13. Rotational hindrance in **7** and absence of this phenomenon in $\text{DmpP}=\text{CCl}_2$. Atomic sizes are relatively estimated in the figure.

2.4.2. UV/Vis Studies

UV/Vis absorption spectra of the newly synthesized *C,C*-dibromophosphaalkenes were recorded to investigate the effect of dimerization on the optical transitions (Figure 14).

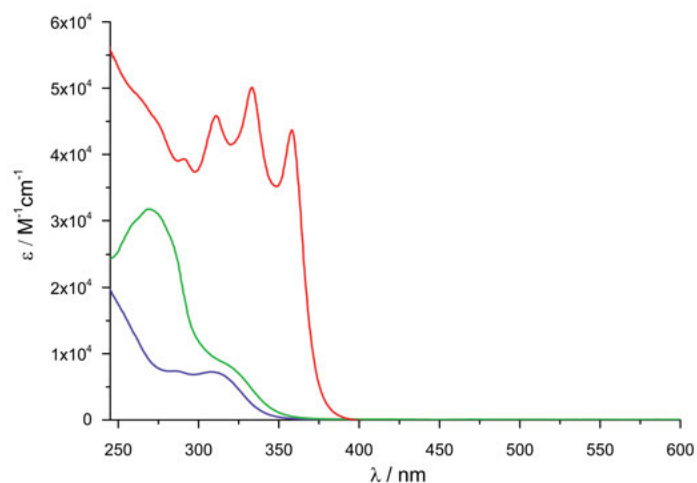


Figure 14. UV/Vis spectra of *C,C*-dibromophosphaalkenes **7** (blue), **9-TIPS** (green), and **11** (red). All spectra were recorded for solutions of the analyte in DCM, 25 °C.

Owing to its extensive π -conjugation, a clear red shift in the lowest energy transition is observed for compound **11** in comparison with monomeric phosphoalkenes **7** and **9-TIPS**. The spectrum of compound **11** is characterized by a fine-structure in the lower energy part of the spectrum, a feature that is often encountered in aromatic planar systems with restricted flexibility. The electronic absorption spectra of **7** and **9-TIPS**, in contrast, are rather featureless, with the spectrum of **9-TIPS** showing a more intense band at 275 nm that is assigned to a $\pi \rightarrow \pi^*$ transition on the acetylene extended Dmp. Apart from this difference, the longest wavelength absorption maximum of phosphoalkene **7** is quite similar to that of **9-TIPS**, indicating that a single acetylenic substitution on the Dmp group shifts this parameter only to a small extent.

2.4.3. Cyclic Voltammetry Studies

Cyclic voltammograms of solutions of the three compounds in CH_2Cl_2 are shown in Figure 15. No waves can be observed in the anodic scans, indicating that all oxidations occur at more positive potential than what is accessible within the solvent window. On the cathodic scans, irreversible reductions

can be observed at a peak potential of $E = -1.83$, -2.07 and -2.13 for **11**, **9-TIPS**, and **7**, respectively. The difference in reduction potential indicates that these processes occur to a large extent on the extended π -conjugated part of the compounds. As expected, compound **11** with the largest π -system is easiest to reduce, followed by the extended acetylenic **9-TIPS**, and finally the unsubstituted **7**.

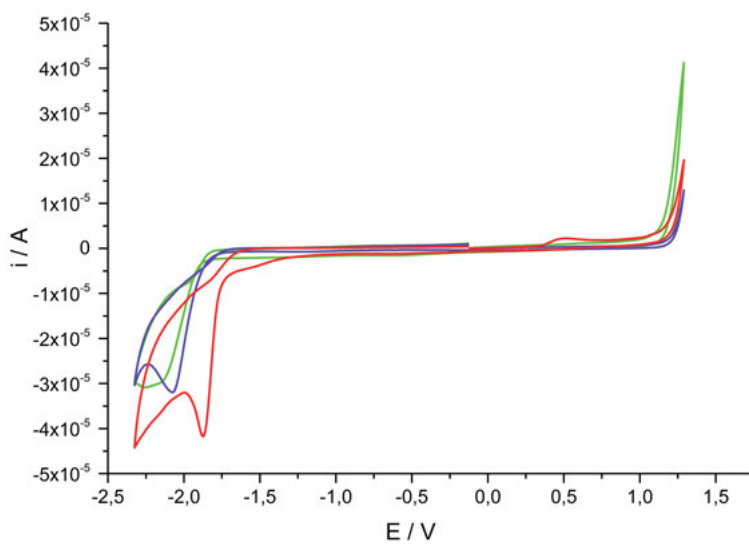


Figure 15. Cyclic voltammograms of *C,C*-dibromophosphaalkenes **7** (blue), **9-TIPS** (green), and **11** (red) (1 mM solutions of compounds in DCM, 0.1 M NBu_4PF_6)

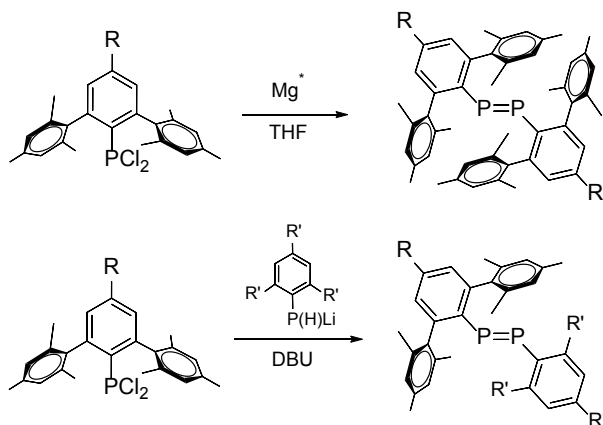
2.5. “Acetylenic” Diphosphenes

Compound **5-Si** is not only useful for making phosphalkenes, but also for the synthesis of a variety of other low-valent phosphorus compounds including diphosphenes. Thus, attempts to synthesize new Dmp-stabilized diphosphenes will be described in this section.

3.5.1. Related Diphosphenes in the Literature

During the past decades, a number of both symmetrical and unsymmetrical diphosphenes which are mainly stabilized by Mes^* or *meta*-terphenyl groups have been reported in the literature.^[29b, 60] Synthesis of the symmetrical diphosphenes is usually achieved by homocoupling of the corresponding dichlorophosphine in the presence of activated Mg (abbreviated as Mg^*). On the other hand, unsymmetrical diphosphenes are mainly obtained by the cross-coupling of a dichlorophosphine and a primary phosphine (Scheme

15). In both of these reactions, elimination of an inorganic salt such as MgCl_2 and LiCl is the driving force for the reaction.



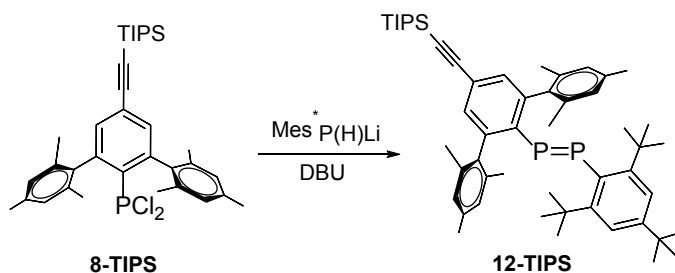
Scheme 15. *Top:* Reductive coupling of the dichlorophosphine by the activated Mg (R = usually H). *Bottom:* Cross coupling of the dichlorophosphine and the lithiated primary phosphine (R' = usually *t*-Bu).

In an alternative synthetic route, phosphanylidene- σ^4 -phosphoranes $\text{ArP}=\text{PMe}_3$ can also drive the reaction towards the formation of the diphosphene products. Such reactions occur through the photolysis of the phospho-Wittig reagent, $\text{ArP}=\text{PMe}_3$, to form a phosphinidene intermediate. The phosphinidene is then either trapped with the same phospho-Wittig reagent to give the symmetrical diphosphene ($\text{ArP}=\text{PAr}$) or with a different reagent, $\text{Ar}'\text{P}=\text{PMe}_3$, to give the unsymmetrical diphosphene product ($\text{ArP}=\text{PAr}'$).^[61]

2.5.2. Synthesis of a New Dmp-Stabilized Diphosphene

A cross-coupled diphosphene bearing a *para*-acetylenic Dmp on one P-center and a Mes^* group on the other was the first synthetic target. The strategy of reducing the dichlorophosphine **8-TIPS** and Mes^*PCl_2 by activated Mg was judged unsuitable as the desired diphosphene would be accompanied by the formation of two symmetrical diphosphenes in a statistical mixture of products. Thus, we decided to use the cross coupling method.

The Mes^* -containing primary phosphine was deprotonated by *n*-BuLi at -50°C to give $\text{Mes}^*\text{P(H)Li}$. The latter was added *in situ* to a solution of **8-TIPS** to form the P-P bond. Addition of DBU at this stage eliminated HCl which led to the formation of the desired product **12-TIPS** (Scheme 16).



Scheme 16. Synthesis of diphosphene **12-TIPS** via the cross coupling of **8-TIPS** and $\text{Mes}^*\text{P(H)Li}$ and a subsequent elimination of HCl . Isolated yield: 21%

The transformations were monitored by ^{31}P NMR spectroscopy and the formation of the $\text{P}=\text{P}$ bond was confirmed by the appearance of two distinct sets of doublets at 453 ppm and 530 ppm with a coupling constant of 574 Hz as shown in Figure 16.

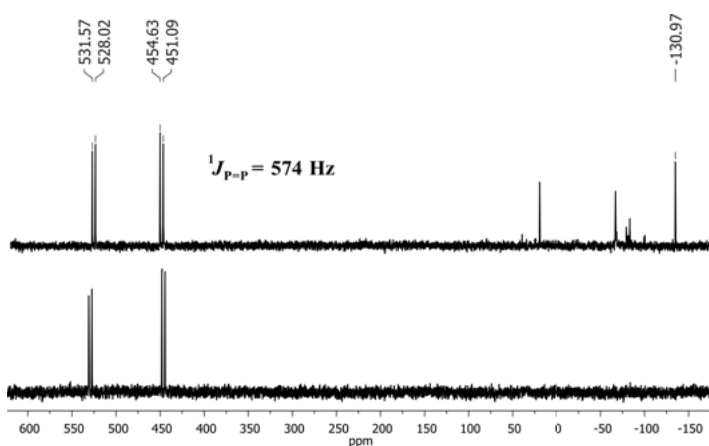
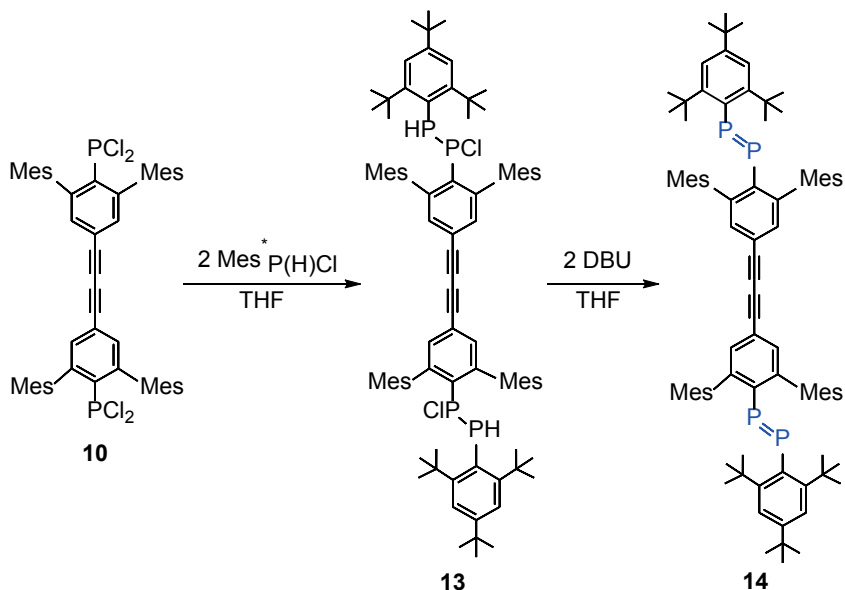


Figure 16. ^{31}P NMR spectra of **12-TIPS**. *Top:* Formation of the diphosphene. The peak at -131 ppm corresponds to Mes^*PH_2 which is regenerated in the reaction due to the presence of trace moisture. *Bottom:* After purification by recrystallization

As the next synthetic target, we used precursor **6** in order to prepare a highly π -conjugated compound with two $\text{P}=\text{P}$ moieties at its termini. In this manner, two equivalents of $\text{Mes}^*\text{P(H)Li}$ were added *in situ* to a solution of **10** in order to make the $\text{P}=\text{P}$ bond. Two equivalents of DBU were added afterwards which led to the formation of the $\text{P}=\text{P}$ bonds (Scheme 17).



Scheme 17. Preparation of bis-diphosphene **14** from bis-dichlorophosphine **10** through intermediate **13**.

The reaction was monitored by ^{31}P NMR spectroscopy. Full consumption of **10** with the disappearance of its singlet at 158 ppm gives rise to the formation of **13** which presents two sets of doublets at -41 ppm and 108 ppm.

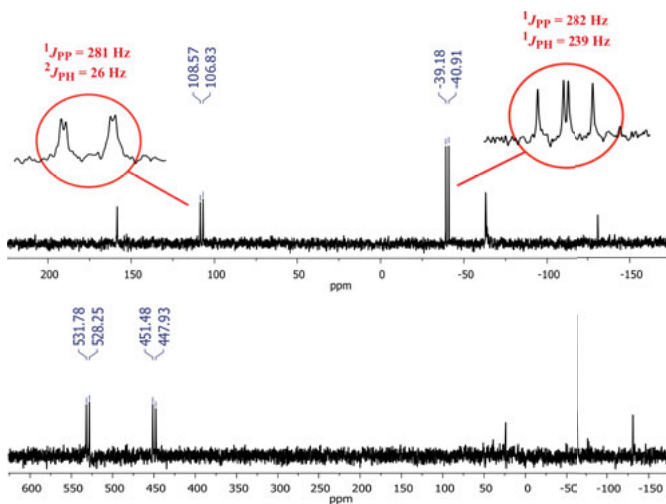


Figure 17. Monitoring the reaction progress by ^{31}P NMR. *Top:* H-coupled ^{31}P NMR showing the formation of **13** with a dd at 108 ppm (${}^1J_{\text{PP}} = 281 \text{ Hz}$, ${}^2J_{\text{PH}} = 26 \text{ Hz}$) and another dd at -41 ppm (${}^1J_{\text{PP}} = 282 \text{ Hz}$, ${}^1J_{\text{PH}} = 239 \text{ Hz}$). *Bottom:* Full consumption of **13** and formation of the desired dimer **14**.

Addition of DBU and elimination of HCl gives the desired bis-diphosphene **14** with its two distinct doublets resonating at 450 ppm and 530 ppm and large J value of 572 Hz. (Figure 17)

Unfortunately, all attempts in the isolation of **14** failed due to a decomposition of the product during the purification process.

2.6. Sequential and Stereoselective Alkynylation of C,C -Dibromophosphaalkenes (Paper III)

Acetylenic phosphalkenes and their classification have already been described in section 2.2. Both C -mono- and C,C -di-acetylenic phosphalkenes have been the center of studies in our group for almost a decade. In 2008, a procedure for the preparation of C,C -diacetylenic phosphalkenes from Mes^*PCl_2 and propargylic reagents was presented.^[21e] However, the stereochemistry of the phosphalkene product was limited and pre-determined by the propargylic reagent. Synthesis of the C,C -diacetylenic phosphalkenes through Sonogashira reactions of $\text{Mes}^*\text{P}=\text{CBr}_2$ is not possible either as the phosphalkyne $\text{Mes}^*\text{C}\equiv\text{P}$ is always obtained as an unwanted product. A dehalogenation via phospho-Fritsch-Buttenberg-Wiechell rearrangement under Sonogashira conditions is the cause for this undesired reactivity.

2.6.1. Development of a Stereoselective Procedure

The alkynylation reaction of olefinic substrates and their similarity to phosphalkenes inspired us to investigate the applicability of this method on the *phospha*-alkenes (Figure 18).

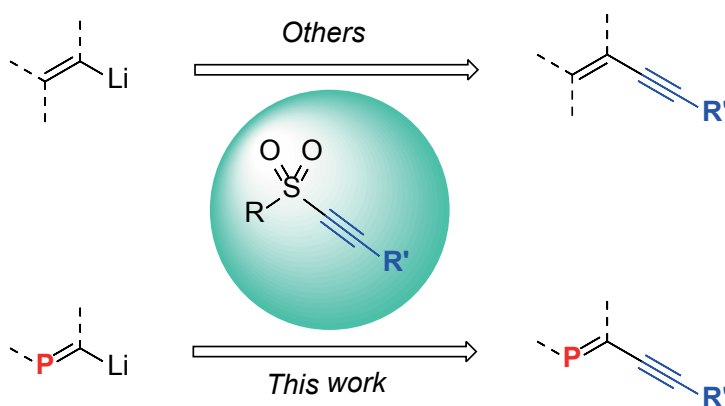
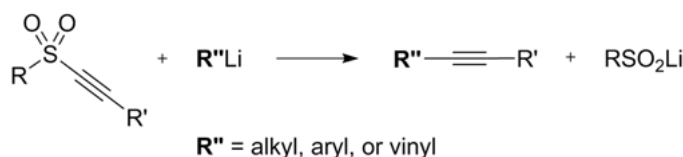


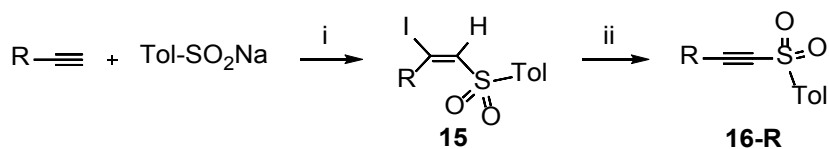
Figure 18. Possible strategy for alkynylation of phosphalkenes inspired by reports on similar reactivity on olefinic systems

In order to transfer acetylenic moieties to lithiated substrates, α,β -acetylenic sulfones have recently been shown to be reliable reagents.^[62] Attack by a nucleophile, usually an organolithium, at the electrophilic C_{sp} of the acetylene gives the alkynylated product and metalated sulfones as the by-product (Scheme 18).



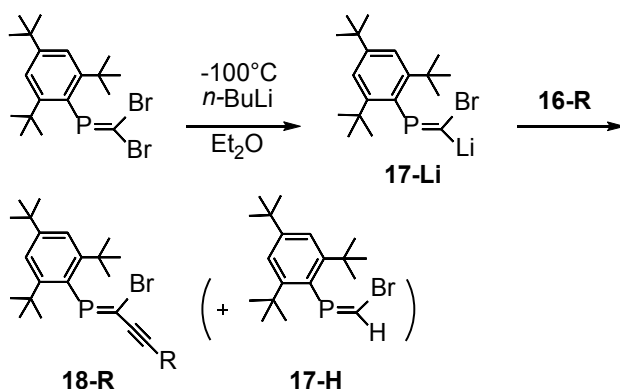
Scheme 18. Formation of $C_{sp}\text{-}C_{sp}^3$ and $C_{sp}\text{-}C_{sp}^2$ bonds via nucleophilic reaction of an organolithium with α,β -acetylenic sulfones

An acetylenic tosylate is the most common reagent for the alkynylation reactions and can be prepared according to literature procedures^[63] (Scheme 19).



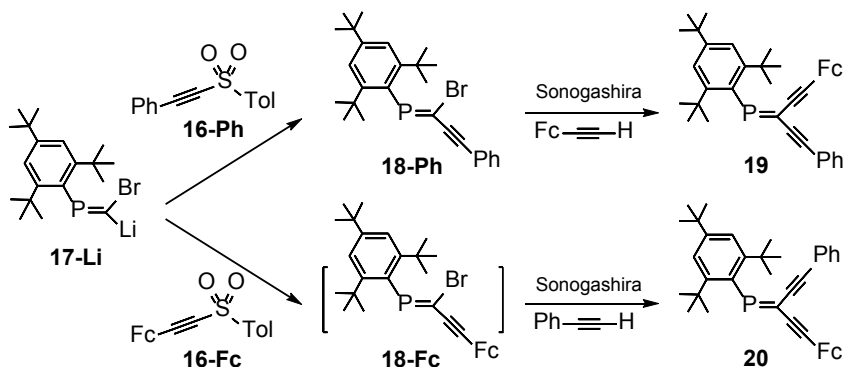
Scheme 19. Preparation of $\text{Ts-C}\equiv\text{C-R}$ **16-R** via elimination of HI from compound **15**. For **16-Ph**: (i) r.t., Tol-SO₂Na, NaI, CAN, MeCN, 59%. (ii) *t*-BuOK, THF, 0 °C, 30 min, r.t., 30 min, 91%.

The alkynylation of phosphalkenes was first tested on $\text{Mes}^*\text{P}=\text{CBr}_2$ which takes advantage of the high kinetic stabilization that Mes^* provides for the molecule. Mono-lithiation of $\text{Mes}^*\text{P}=\text{CBr}_2$ by the addition of BuLi at -100 °C initiates the sequence and gives the *cis*-lithium phosphacarbenoid **17-Li** selectively. If the lithiation is conducted at higher temperatures, a mixture of *cis*- and *trans*-lithium phosphacarbenoids is usually obtained. The acetylenic tosylate, Tol-SO₂-C≡C-R (R = Ph, 4-BrC₆H₄, and Fc), was added to **17-Li** at this stage to afford the alkynylated phosphalkenes **18-R**. Unfortunately, the protonated phosphalkene **17-H** was also observed in most of the attempts, and undesired side-product that may arise from the presence of small amounts of moisture in the reaction (Scheme 20).



Scheme 20. Successful alkylation of $\text{Mes}^*\text{P}=\text{CBr}_2$ with α,β -acetylenic sulfone **16-R** ($\text{R} = \text{Ph}$, $4\text{-BrC}_6\text{H}_4$, and Fc). The hydrolyzed phosphalkene **17-H** was also formed as a minor product in the reaction.

In order to prove the stereochemical control over the products, we conducted a subsequent Sonogashira reaction on the *C*-acetylenic phosphalkenes. By this method, *C,C*-diacetylenic phosphalkene final products were obtained stereoselectively as shown in Scheme 21.

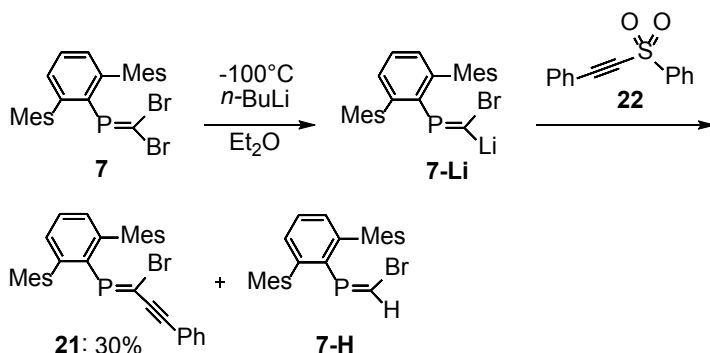


Scheme 21. Stereochemical control over the final *C,C*-diacetylenic phosphalkene products. Isomers **19** and **20** were obtained through two separate reactions with full control over the stereochemical outcome.

2.6.2. Application of the Method on the Dmp-Stabilized Phosphaalkenes

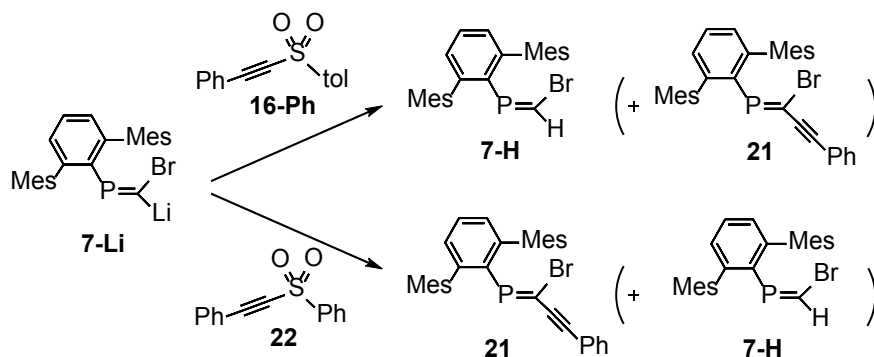
We were curious to determine whether or not the reaction would also work for phosphalkenes with protecting groups other than Mes^* in order to expand the substrate scope. $\text{DmpP}=\text{CBr}_2$ **7** which benefits from the kinetic stability of the Dmp group was thus targeted. Phosphaalkene **7** was monolithiated in the same way as described for $\text{Mes}^*\text{P}=\text{CBr}_2$. The resulting lithiat-

ed species **7-Li** was formed selectively, and the suitable sulfoneacetylene reagent was subsequently added. The alkynylated product **21** was obtained as the major product along with **7-H** as the minor product (Scheme 22). Purification by column chromatography afforded the pure product free of **7-H** impurity although the isolated yield (30%) was low, due to slow decomposition of the compound on the column.



Scheme 22. Formation of C-acetylenic phosphoalkene **21** via the reaction of phenyl sulfonyl reagent **22**, prepared as described in Scheme 19 in 50-60% isolated yields, with the lithiated phosphoalkene **7-Li**.

It is important to note that the *tosylated* reagent gave mainly **7-H** as the major product and the desired compound **21** formed only as the minor component. However, using a *phenyl* sulfonyl reagent enhanced the reaction significantly as 81% conversion of **7** to **21** was accomplished according to ^{31}P NMR spectroscopy (Scheme 23).



Scheme 23. Significant impact of the acetylenic reagent on the reaction outcome. A simple change of the tosyl group in **16-Ph** to a phenyl sulfonyl group in **22** improved the conversion dramatically and afforded the desired phosphoalkene **21** in 30% isolated yield.

Interestingly, the reaction of $\text{Mes}^*\text{P}=\text{CBr}_2$ with the phenyl sulfonyl reagent **22** was also improved as compared to the reaction with the tosylated reagent **16-Ph** and a high conversion of 85% (^{31}P NMR yield) was achieved.

2.7. Outlook

As mentioned in the beginning of the chapter, *C,C*-dihalophosphaalkenes are invaluable compounds from which various synthetic targets can become accessible.

The *C,C*-dibromophosphaalkenes described herein can potentially be used for synthesizing diverse low-valent phosphorus compounds. Among them, one could imagine a variety of phosphalkenes with diverse $\text{P}=\text{C}<$ substituents. Such phosphalkenes can subsequently be further functionalized at their acetylene termini to introduce further functionality. The molecules are therefore extendable at both the carbon and phosphorus terminus of the $\text{P}=\text{C}$ bond. As a result, novel and elaborate π -conjugated architectures for potential applications in organic electronics can be conceivable, which leaves great breadth for future investigations.

We have shown that dichlorophosphine precursors **8-TIPS** and **10** can be used in the synthesis of diphosphenes. Symmetric and unsymmetric diphosphenes with a Dmp moiety have previously been synthesized by different research groups. However, many advanced $\text{P}=\text{P}$ -containing systems can in theory be synthesized with the two new protecting systems that we have developed. As a result, intriguing highly π -conjugated diphosphenes or $\text{P}=\text{P}$ -containing polymers are among potential future synthetic targets.

One of the most common ways for making phosphalkynes is via the phospho-FBW rearrangement of *C,C*-dihalophosphaalkenes. Although $\text{Dmp-C}\equiv\text{P}$ has been previously synthesized by Jones and colleagues, new $\text{P}\equiv\text{C}$ -containing systems are expected to become accessible from *C,C*-dibromophosphaalkenes **9-TIPS** and **11**. Such phosphalkynes are in theory very interesting π -conjugated systems since one could imagine their use as molecular wires.

Compounds **5-Si** and **6** were used for the synthesis of new *C,C*-dibromophosphaalkenes and diphosphenes in this thesis. However, these compounds also open up a variety of synthetic possibilities not only in phosphorus chemistry, but also for other main group elements such as arsenic, bismuth, silicon, *etc.* Having such a potentially broad application scope, compounds **5-Si** and **6** can be considered as precursors for future investigations in other branches of main group chemistry and single molecule electronics.

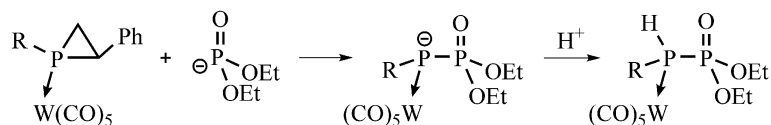
3. Metal-free Phosphanylphosphonate and Transition Metal-free Phospha-HWE Reaction (Paper IV)

Prior to this work, phospha-HWE reactions have been limited to phosphanylphosphonates to which a metal-center has been coordinated. The resulting products of these reactions are phosphaalkenes which carry this metal fragment at the P-center. We describe herein the synthesis and isolation of the first metal-free phosphanylphosphonate and its successful use in transition metal-free phospha-HWE reactions under mild conditions and with a broad substrate scope.

3.1. Metal-coordinated Phosphanylphosphonates

As already mentioned in section 1.2.3, phosphanylphosphonates play a key role in phospha-HWE reactions to transform carbonyl compounds to phosphaalkenes. These molecules are generally unstable as their P(III) center is highly reactive towards moisture. Therefore, means that can lead to protection of this center against oxidation or hydrolysis are essential for the synthesis and isolation of these compounds. The classical method is the coordination of a metal-center to the P(III) lone pair of the phosphanylphosphonates which renders the compounds isolable.

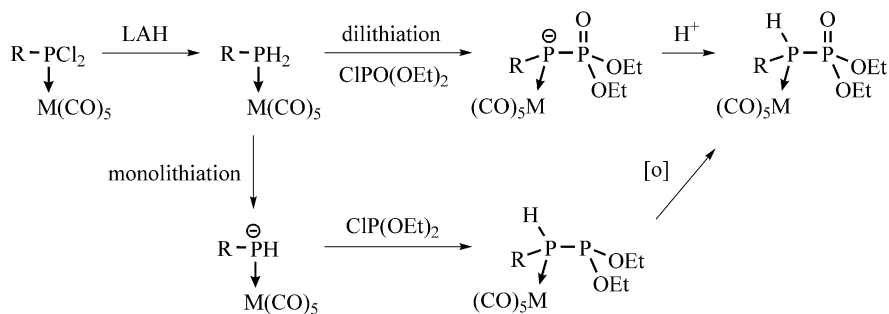
The very first example was a phosphanylphosphonate with a P(III) center coordinated to a $W(CO)_5$ fragment, which was derived from its corresponding phosphirane.^[43] (Scheme 24)



Scheme 24. First reported phosphanylphosphonate by Mathey *et al*

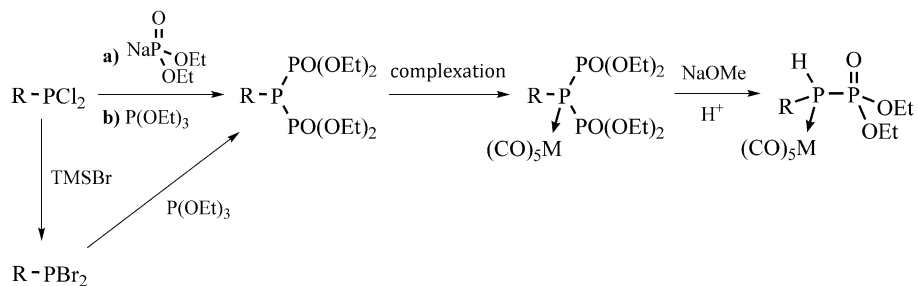
In an improved approach, a metal-coordinated dichlorophosphine was reduced to a primary phosphine which was doubly lithiated afterwards. Reaction of the lithiated species with diethyl chlorophosphate gave the metal-

complexed phosphanylphosphonate (M = W or Mo).^[64] The primary phosphine can be also *mono*-lithiated to react with diethyl chlorophosphite to give an intermediate with two P(III) centers. Oxidation of the latter leaves the complexed P-center intact while oxidizing the uncomplexed P-center to P(V), thereby affording the desired phosphanylphosphonate.^[65]



Scheme 25. Improved methods for making phosphanylphosphonates

In a more generalized approach, with a wider scope for the R group and M, two P(V) centers were introduced onto an uncomplexed dichlorophosphine starting material which was *later* complexed to a metal fragment. Cleavage of one of the P-P bonds and a subsequent protonation furnished the desired phosphanylphosphonate (Scheme 26, **a**).^[65] However, preparation of NaOP(OEt) is quite tedious as the amount of Na needs to be precise otherwise the excess of Na reduces the dichlorophosphine starting material.



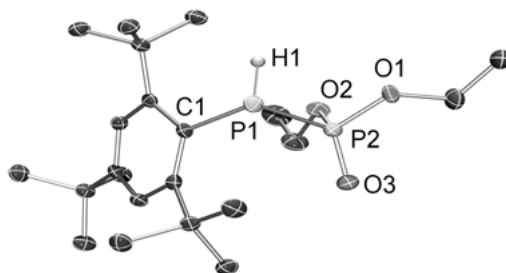
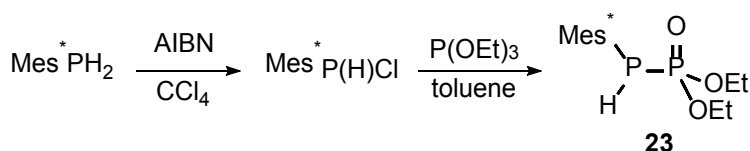
Scheme 26. More reliable pathways to phosphanylphosphonates reported by Mathey *et al* and our group

A phosphinodiphosphonate intermediate can also be produced by a Michaelis-Arbuzov reaction from either a dichloro- (Scheme 26, **b**) or dibromophosphine starting material. This procedure developed by our group, offers a reliable protocol for the multi-gram preparation of metal-coordinated phosphanylphosphonates in good overall yields.^[66]

3.2. Isolation of the First Metal-free Phosphanylphosphonate

Prior to this work, metal coordination was the only reported method for the stabilization of phosphanylphosphonates in *phospha*-HWE reactions where phosphalkene complexes are afforded as products. Such metal fragments block the lone pair of the phosphorus atom for post-synthetic reactions. This drawback as well as the tedious removal of the metal fragment from the phosphalkene products provoked us to design a phosphanylphosphonate which is free of metal and at the same time stable and isolable.

In chapter 2, various bulky groups were mentioned which can provide sufficient steric protection to stabilize phosphalkenes kinetically. We hypothesized that utilizing such stabilizing groups could be a novel way to provide stability for phosphanylphosphonates and eventually phosphalkene products. Among the various options, we chose Mes* as the protecting group to serve this purpose. Mes*PH₂ is a very stable primary phosphine and can be prepared in high yields according to the known methods.^[67] Mes*PH₂ can be chlorinated with CCl₄ under a radical mechanism to afford the secondary phosphine Mes*PHCl.^[68] The latter can undergo a “*phospha*-Michaelis-Arbuzov” reaction to afford the desired phosphanylphosphonate (Scheme 27).



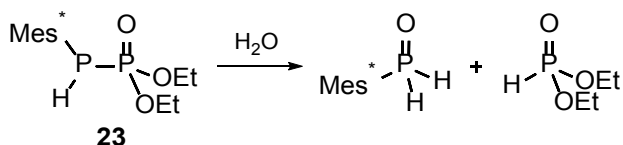
Scheme 27. Synthesis of phosphanylphosphonate **23** with its ORTEP plot. All hydrogen atoms not associated with P(III) center are omitted for clarity.

The transformations depicted in Scheme 26 were monitored by ³¹P NMR spectroscopy. The spectrum of Mes*PH₂ shows a characteristic peak at -131 ppm that is quantitatively transformed to a signal at 21 ppm which is assigned to Mes*PHCl. The final transformation produces a product the NMR

spectrum of which shows a characteristic set of doublets at 35 and -89 ppm ($^1J_{PP}$ of 222 Hz), indicating full formation of phosphanylphosphonate **23**.

Besides the characteristic signals of the compound in the ^{31}P NMR spectrum, ^1H NMR also exhibits a distinctive doublet of doublets at 5.4 ppm which stems from the coupling of the proton to the two phosphorus atoms ($^1J_{HP} = 231$ Hz and $^2J_{HP} = 14$ Hz). In addition, two broad signals are observed both in the aliphatic and aromatic regions due to the hindered rotation of the Mes* group in the molecule that leads to broadening of the signals for *ortho*-*t*-Bu groups and *meta*-protons, respectively. Such broadening of signals is clearly visible in the ^{13}C NMR spectrum of the compound as well.

Phosphanylphosphonate **23** is prepared on a multi-gram scale in high overall yields (60-75%) and can be stored under inert gas in the freezer for long periods of time without any sign of decomposition. If exposed to moisture, water can attack the P(III) center as a nucleophile and cause slow decomposition of the compound. (Scheme 28)



Scheme 28. Decomposition of phosphanylphosphonate **23** when exposed to moisture

The decomposition products were assigned on the basis of the proton-coupled ^{31}P NMR spectrum depicted in Figure 19. The spectrum shows a triplet at -9 ppm and a doublet at -28 ppm which are assigned to Mes*P(O)H₂ and HP(O)(OEt)₂, respectively. These peaks have coupling constants ($^1J_{PH}$) of 482 Hz and 577 Hz which are in the typical range of direct P-H bonds (Figure 15).

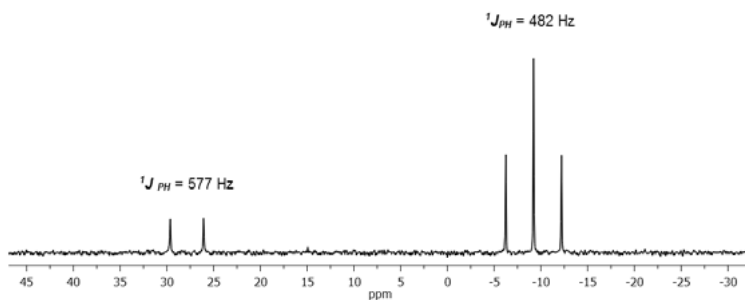
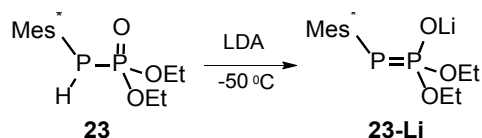


Figure 19. Triplet and doublet signals assigned to Mes*P(O)H₂ and HP(O)(OEt)₂, respectively

3.3. Transition metal-free Phospha-HWE Reaction

Phosphanylphosphonate **23** is an excellent reagent for the transition metal-free phospha-HWE reaction due to its straightforward synthesis, stability, and the fact that it can be stored over extended periods of time. Since there is no metal fragment on the molecule, metal-free phosphaalkenes are furnished as final products.

Deprotonation of phosphanylphosphonate **23** by adding LDA to its THF solution at $-50\text{ }^{\circ}\text{C}$ initiates the reaction. The reaction is accompanied by a characteristic color change from colorless to bright yellow and complete within seconds (Scheme 29).



Scheme 29. Deprotonation of **23** with LDA and formation of enolate **23-Li**

A significant impact on the chemical shifts is observed in ^{31}P NMR as the phosphanylphosphonate transforms to its enolate form (Figure 20). The difference in ^{31}P chemical shifts for enolate **23-Li** ($\Delta\delta = 189\text{ ppm}$) is considerably larger than that of **23** ($\Delta\delta = 125\text{ ppm}$). More interestingly, there is a dramatic increase in the coupling constant ($^1J_{\text{P-P}}$) from 222 Hz (**23**) to 615 Hz (**23-Li**). The latter is in the same range as those of phosphanylidene- σ^4 -phosphoranes and indicates the high double bond character between the two P centers in the enolate.

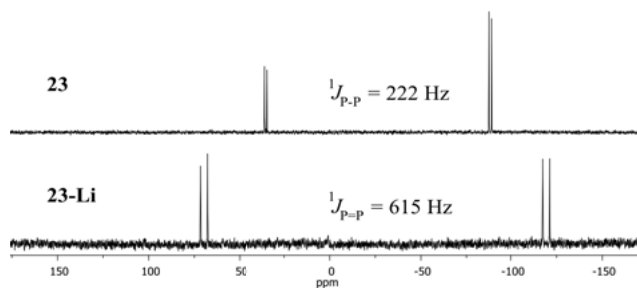


Figure 20. Significant impact of deprotonation on the chemical shifts and coupling constant

Furthermore, comparison between enolate **23-Li** and its M-coordinated (M= W, Mo) analogues reveals that the coupling constant in the latter ($^1J_{\text{P-P}} = 390\text{ Hz}$) is significantly smaller than that of **23-Li** ($^1J_{\text{P-P}} = 615\text{ Hz}$). (Figure 21)

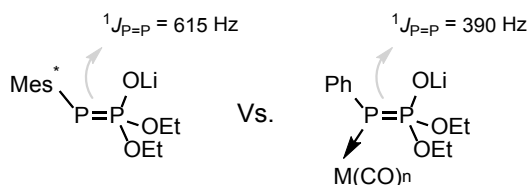


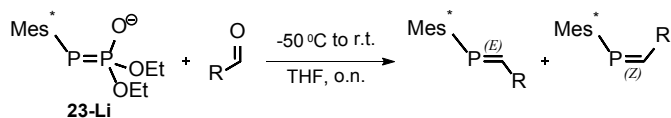
Figure 21. The impact of metal coordination on P-P coupling constant; a significantly higher J value for the metal-free enolate

One reason for this phenomenon is likely π -backdonation from the transition metal to the $P=P \pi^*$ antibonding orbital which leads to a decrease in bond order and, consequently, coupling constant. A second plausible reason is that metal-coordination blocks the lone pair on the P(III) from contributing to negative hyperconjugation, which also decreases the bond order and $^1J_{PP}$ coupling.

3.3.1 Substrate Scope

An assorted selection of aldehydes including aliphatic, aromatic, vinylic and heterocyclic systems was chosen to react with enolate **23-Li** in order to test the *phospha*-HWE reaction and to show its substrate scope (Table 1).

Table 1. Phospha-HWE reaction of aldehydes to the corresponding phosphalkenes



| Aldehyde | <i>E</i> -Phosphaalkene | No. | Conversion [%] | <i>E/Z</i> | Yield [%] |
|----------|-------------------------|-----------|----------------|---------------|-----------|
| | | 24 | 64 | Only <i>E</i> | 49 |
| | | 25 | 100 | 84:16 | 96 |
| | | 26 | 91 | 87:13 | 70 |
| | | 27 | 89 | 92:8 | 65 |
| | | 28 | 72 | 81:19 | 40 |


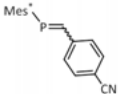
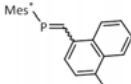

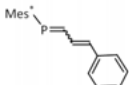
Almost all reactions were complete overnight, with high conversions and good isolated yields except for the reaction of **23-Li** with isobutyraldehyde which needed longer reaction times. The reaction was stereoselective towards *E*-phosphaalkenes with high *E/Z* ratios in all cases. In the reaction of isobutyraldehyde, *E*-**24** was the sole product which is most likely due to the bulkiness of the isopropyl group that restrains the formation of the *Z*-isomer. Although the isolated yield with this aldehyde was not high, it is still important to note that the reaction despite of the bulkiness of the aldehyde. The highest isolated yield was obtained in the reaction of 4-cyanobenzaldehyde indicating that electron-withdrawing systems probably react better in *phospha*-HWE reaction.

3.3.2. *E/Z* Isomerization of Phosphaalkene Products

A common phenomenon that we noticed among the phosphaalkene products was that they tend to undergo *E/Z* isomerization post-synthetically. The exception is *E*-**24** in which the bulkiness of the isopropyl moiety prevents the formation of the *Z*-isomer. Isomerization in **25-28** is probably originating from different sources. Light (or heat) can be one of the sources since the proportion of the *Z*-isomer increases with longer reaction times. Column chromatography on acidic silica also proved to promote isomerization as the *E/Z* ratios decreased during purification. The most extreme case was experienced with the more fragile phosphaalkene **28** which did not survive the conditions of column chromatography and a high degree of decomposition and *E/Z* isomerization was observed.

³¹P NMR analyses of the phosphaalkenes showed that *E*-phosphaalkene resonances are generally shifted downfield in comparison to their *Z*-phosphaalkenes. *E*-**25**, *E*-**26**, *E*-**27**, and *E*-**28** resonate at 284, 259, 247 and 269 ppm, respectively, which is considerably downfield in comparison with their *Z*-congeners ($\Delta\delta = 19, 16, 22$ and 17 ppm, respectively) (Table 2). A similar trend is observed in the ¹H NMR spectra as the P=C(*H*) protons in *E*-products resonate downfield compared with those of *Z*-products. These protons show a doublet with ²*J*_{HP} in the range of 24-26 Hz in *E*-phosphaalkenes, which is clearly smaller than that of *Z*-phosphaalkenes in the range of 35-38 Hz.

Table 2. Distinct difference in $^2J_{\text{HP}}$ values and ^{31}P chemical shifts between *E*- and *Z*-isomers

| Phosphaalkene | No. | $^2J_{\text{HP}}$ [Hz] | | ^{31}P [ppm] | |
|---|-----------|------------------------|----------|-----------------------|----------|
| | | <i>E</i> | <i>Z</i> | <i>E</i> | <i>Z</i> |
|  | 24 | 26.0 | - | 241 | - |
|  | 25 | 25.0 | 37.0 | 284 | 265 |
|  | 26 | 25.4 | 35.7 | 259 | 243 |
|  | 27 | 24.0 | 35.3 | 247 | 225 |
|  | 28 | 24.1 | 37.8 | 269 | 252 |

In the case of naphthalene-containing phosphaalkene **26**, both light and acidic silica induced isomerization occurs to a large extent. Pure crystals of *Z*-**26** suitable for single crystal X-ray diffraction were obtained by slow evaporation of DCM/MeCN solutions (Figure 22). It is noteworthy that this crystal structure is one of the few examples known for uncoordinated acyclic *Z*-phosphaalkenes.^[34b, 69]

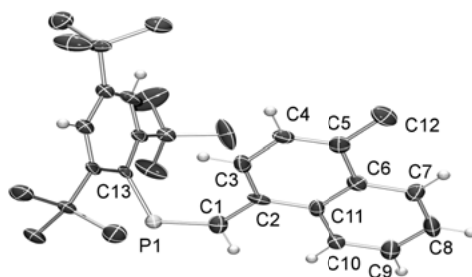


Figure 22. ORTEP plot of *Z*-**26**. Aliphatic hydrogens are omitted for clarity.

Interestingly, the ^1H NMR spectrum of *Z*-**26** exhibits a doublet of doublets at 5.7 ppm assigned to $\text{C}_3(\text{H})$, which is quite up-field for typical aromatic protons. This dramatic shift is due to the anisotropic effect of the Mes^* group as H_{C_3} is located above its phenyl ring. A similar but less intense effect is ob-

served for H_{C4} since this proton is spatially farther from Mes^* . Also, H_{C4} is too far from the phosphorus center to show observable coupling, and is thus observed as a doublet due to its coupling to H_{C3} . Similar anisotropic effect and splitting patterns are observed also for *Z*-**25** with a doublet of doublets at 6.2 ppm and a doublet at 7.2 ppm. (Figure 23)

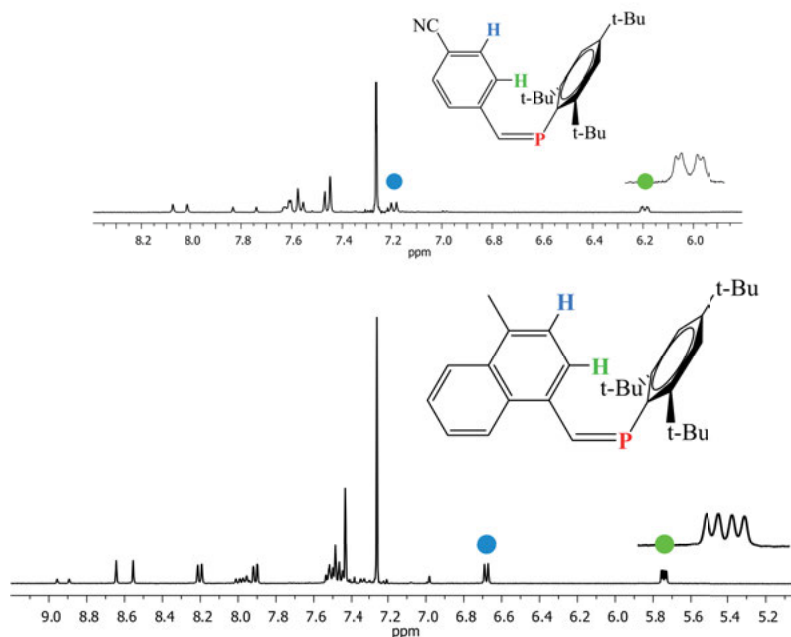


Figure 23. Explanation for the upfield chemical shifts of the assigned aromatic protons in *Z*-**25** (top) and *Z*-**26** (bottom)

3.3.3. Successful application of a Chromatography-free Purification Method on Phosphaalkenes

As previously mentioned, purification of *E*-phosphaalkene products by column chromatography leads to partial isomerization to *Z*-phosphaalkenes and a decrease in *E/Z* ratios. Unfortunately, purification of phosphaalkene **28** by column chromatography dropped the overall isolated yield to an extent that we were not able to isolate the product. Therefore, an alternative purification method for that particular phosphaalkene needed to be devised. Gilheany and colleagues recently reported a mild and convenient chromatography-free purification method for the products of Wittig and Appel reactions.^[70] They introduced a facile procedure using oxalyl chloride to react with the phosphine oxide by-product while leaving the alkene intact throughout the purification process. Their results promoted us to apply the method on *phospha-*

alkenes to find out whether or not $P=C$ bonds can survive the applied conditions.

We started our investigation with the more stable phosphalkene **25**. Gratifyingly, oxalyl chloride addition to the crude phosphalkene **25** followed by stirring for 1 h showed no sign of the reaction of oxalyl chloride with the $P=C$ bond. The oxalyl chloride treatment for purification purposes is superior to column chromatography on acidic silica as the former retains the high E/Z ratio while the latter diminishes this ratio to a considerable extent (Figure 24).

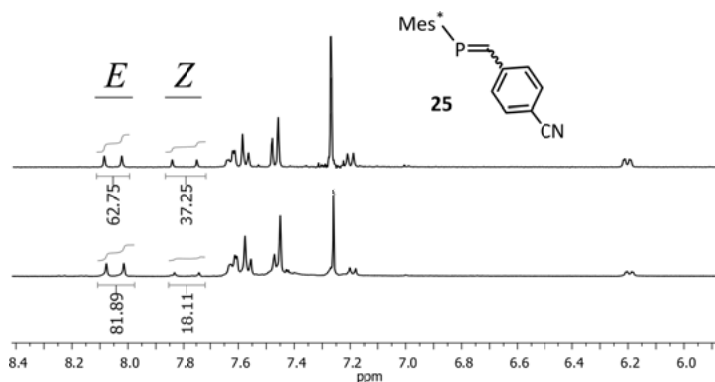


Figure 24. The NMR spectra of the pure E/Z -**25** belonging to two different experiments, comparing the stereochemical outcome between purification by column chromatography (top) and oxalyl chloride treatment (bottom)

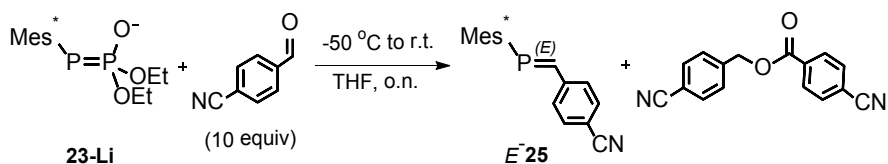
Fortunately, also phosphalkene **28** survived the purification conditions and all $P=O$ -containing species could be filtered off after the addition of oxalyl chloride. Eventually, slow evaporation of DCM/MeCN solution of the resulting residue afforded pure recrystallized E -**28** in 40% isolated yield.

3.4. Side-reactions of phospho-HWE Reaction

Side reactions in organic/inorganic chemistry are not unexpected phenomena and the *phospha*-HWE reaction is not an exception. In the reaction of 4-cyanobenzaldehyde with *phospha*-HWE reagent **23**, two types of side-products were observed.

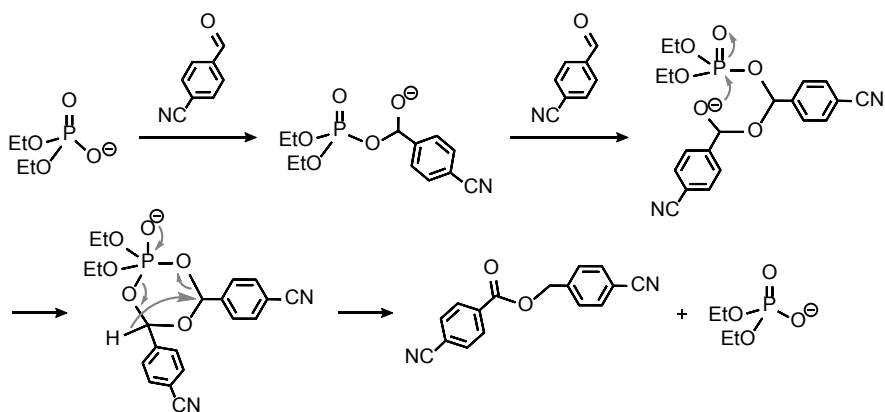
Esterification/Dimerization of Aldehydes

During one attempt in the reaction of **23-Li** with 4-cyanobenzaldehyde, a dimeric compound was obtained in addition to the desired phosphalkene E -**25** (Scheme 30).



Scheme 30. Dimerization of 4-cyanobenzaldehyde to the ester side-product

As our conditions for the *phospha*-HWE include an excess of aldehyde (typically 4 equivalents), we believe that the observed ester by-product arises from the unreacted aldehyde that is left after phosphoalkene formation. Mechanistically, a Tishchenko-type of reaction can be considered.^[71] As depicted in Scheme 31, the diethyl phosphate by-product from the *phospha*-HWE reaction can react with two equivalents of aldehyde to form an intermediate that undergoes intramolecular cyclization by taking advantage of the electrophilicity (and oxophilicity) of the phosphorus atom. The resulting 6-membered ring undergoes a 1,3-hydride shift and collapses to the ester and diethyl phosphate. In this way, the reaction is in fact catalytic on diethyl phosphate.

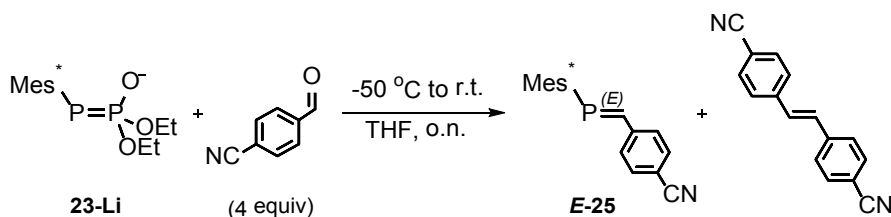


Scheme 31. Plausible mechanism of esterification side-reaction

Formation of the ester does not harm the outcome of the *phospha*-HWE reaction as it occurs only after the phosphoalkene product and diethyl phosphate by-product are formed in the reaction. However, having such a side-product can make purification of the phosphoalkene more complicated and time-consuming. Such a dimeric side-product was never observed in the modified procedure that will be described in section 3.5.

Enthralling side-product and build-up for the Succeeding Investigation

During optimization of the *phospha*-HWE reaction with 4-cyanobenzaldehyde, white crystals of another compound were isolated, although in very low yield (5%). NMR analysis of the obtained blue fluorescent compound revealed that this product is in fact *E*-4,4'-(ethene-1,2-diyl)dibenzonitrile (Scheme 32).



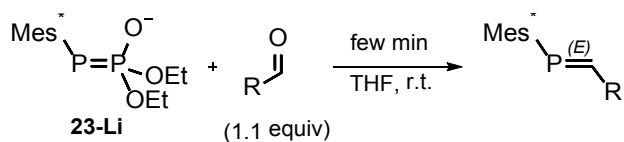
Scheme 32. Formation of the olefinic side-product in *phospha*-HWE reaction

This finding massively attracted our attention and inspired the studies that are subject of in the next chapter.

3.5. Modified Reaction Conditions

Subsequent to the published paper IV, reaction conditions were modified by changing a few simple factors. First, the phosphanylphosphonate reagent and the aldehydes were dried over P₂O₅ under vacuum (or distilled) to ensure rigorous exclusion of moisture in the reaction. Second, freshly-prepared LDA replaced the commercially purchased LDA. Third, LDA was added at room temperature to THF solutions of **23**, rather than at reduced temperatures. Finally, the reaction was conducted in the absence of light to minimize *E/Z* isomerization of the phosphalkenes.

In this fashion, the outcome of the *phospha*-HWE reaction was enhanced dramatically. First, reaction times were reduced from typically overnight to just a few minutes. Second, quantitative conversion of **23-Li** to the phosphalkene products was obtained. Third, much higher *E/Z* ratios were achieved since the reactions were carried out in the dark and reaction times were extremely short. As a matter of fact, only trace or even no *Z*-product was observed in most cases. Finally, none of the side-products mentioned in the previous section were ever observed under the improved conditions (Scheme 33).



Scheme 33. The modified reaction benefits from mild conditions such as room temperature and short reaction time

These new results were confirmed by repeating some of the reactions from Table 1 with the modified conditions. *E*-phosphaalkene products were exclusively formed with trace or no sign of *Z*-isomer, as monitored by ^{31}P NMR. We even tested a few more aldehydes and subjected them to the modified reaction conditions, which pleasantly gave similar results. For instance, the corresponding phosphaalkenes of benzaldehyde, 3,5-dimethoxybenzaldehyde, 3,5-di-*t*-butylbenzaldehyde, trimethylacetaldehyde, and 6-Bromo-2-pyridinecarboxaldehyde were exclusively formed, resonating at 258, 259, 260, 240, and 293 ppm in ^{31}P NMR spectra, respectively.

4. A Novel Entry into C=C Bond Formation via Organophosphorus Chemistry (Paper V)

The importance of alkenes and their applications in our lives is unquestionable. They are major feedstock materials for many industrial uses. Alkenes and their polymerization are essential for manufacturing plastics, and C=C bonds are present in numerous other compounds from drugs and vitamins to pigments and lipids. Therefore, devising new and innovative reactions towards the synthesis of alkenes is at core of the organic chemistry and of great significance. This chapter is devoted to our discovery of a new methodology for the reductive coupling of aldehydes into alkene products, where organophosphorus chemistry plays a key role in its development. Mechanistic studies and substrate scope of the method will be discussed in detail. Advantages and limitations of our coupling method will be highlighted and an outlook of the project presented.

4.1. Synthetic Routes to 1,2-Disubstituted *E*-alkenes from Aldehydes

There are various synthetic routes from feedstock aldehydes to 1,2-disubstituted *E*-alkenes in organic chemistry. These reactions are depicted in Scheme 34 and briefly discussed in the following section:

Wittig Reaction

As discussed in chapter 2, the Wittig reaction is one of the most common ways to make alkenes. A phosphonium ylide is the reagent that reacts with aldehydes to give the corresponding alkenes. If stabilized by an anionic stabilizing group, the phosphonium ylide favors the *E*-alkene product. If the phosphonium ylide is non-stabilized, some of the *E*-selectivity is compromised, but can be recovered by conducting the reaction under Schlosser's modification.

Horner-Wadsworth-Emmons Reaction

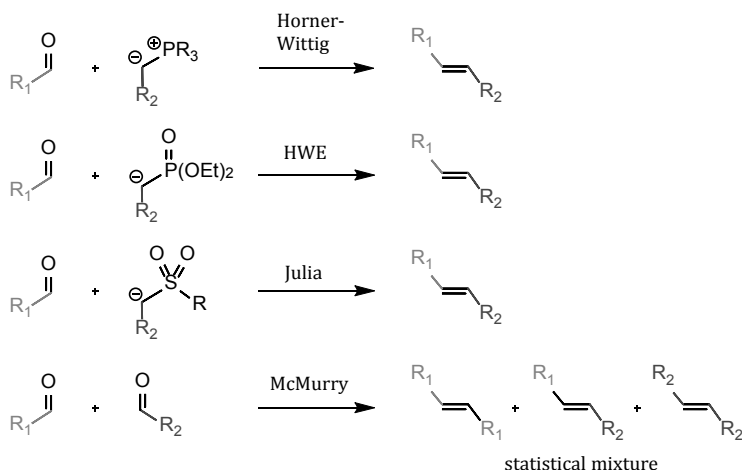
Another widely used method to make alkenes is the HWE reaction, a modification of the classical Wittig reaction. Being more nucleophilic than their corresponding phosphonium ylides, phosphonate-stabilized carbanion reagents react with aldehydes and give preferentially the *E*-alkene products.

Julia Olefination

Highly *E*-selective Julia olefination occurs via a radical mechanism and benefits from high functional tolerance and mild conditions. A sulfone carbanion reacts with aldehydes to afford an intermediate alcohol. Further functionalization of the latter, followed by a reductive elimination step gives rise to the alkene product in the end.^[72] Julia-Kocienski olefination is the modified version of this reaction which conducts the transformations in one step.^[73]

McMurry Coupling

McMurry coupling is the only method among those mentioned which *directly* couples two aldehydes to the alkene product.^[74] This reductive coupling is carried out using a low-valent titanium reagent and occurs via a radical mechanism with consecutive electron transfer steps which eventually gives the alkene product and TiO₂ as a by-product. The coupling has a rather wide substrate scope and is usually used for homocoupling of aldehydes. As there is no intrinsic selectivity in the McMurry reaction, the coupling of two different aldehydes always gives a statistical mixture of *E*-alkene products. In this manner, McMurry coupling is known more as a homocoupling rather than a cross coupling method.

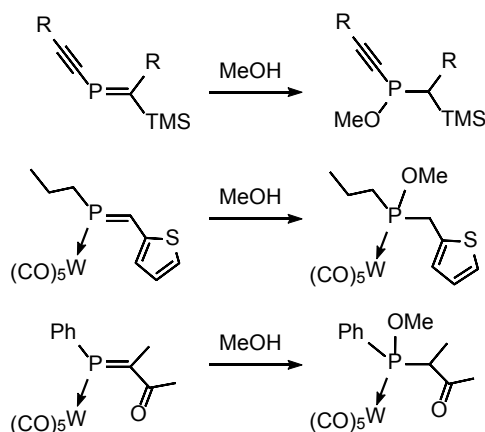


Scheme 34. Synthetic methods in literature to produce 1,2-substituted *E*-alkenes from aldehydes

4.2. Phosphaalkenes as Electrophiles

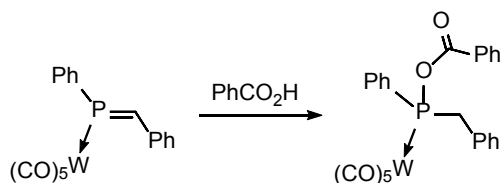
As described in Chapter 1, phosphorus atoms are more electropositive than carbon which makes the P=C bond in phosphaalkenes slightly polar, leaving the phosphorus atom with a partial positive charge. In this manner, the phosphorus center of the P=C bond is electrophilic and prone to attacks from nucleophiles.

There are many examples of nucleophilic reactions with the P=C bond in the literature. One of the most common examples of such reactions is trapping of phosphaalkenes with methanol which produces the corresponding phosphinites (Scheme 35). A methoxy group always ends up on the P-center to make the strong P-O bond while the C-center carries a proton.^[56, 64, 75]



Scheme 35. Examples of phosphaalkene trapping by methanol

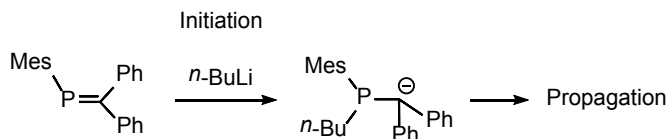
Another interesting example is the addition of benzoic acid across the P=C bond in a base-catalyzed process.^[75] In this addition, the benzoate reacts with the P-center leading to the formation of P-O and C-H bonds. (Scheme 36)



Scheme 36. An example for trapping of phosphaalkenes with benzoic acid

Gates *et al.* exploited the electrophilicity of the P=C bond in their anionic polymerization studies.^[28, 31, 76] They activated the P=C of their phosphaalkene monomer by adding nucleophilic *n*-BuLi as an initiator. The initiated

species could then react with another monomer and start propagation at ambient temperature. (Scheme 37)



Scheme 37. Exploiting the electrophilicity of phosphalkene in anionic polymerization

Unstable phosphalkenes and their decomposition by moisture is a known phenomenon. Hydrolysis of phosphalkenes is in fact another example of the electrophilic P=C reacting with nucleophiles. Formal addition of water occurs on phosphalkenes with insufficient kinetic stabilization to give the corresponding secondary phosphine oxide (SPO) decomposition product. Similar to the hydrolysis of esters, phosphalkenes can be hydrolyzed under either acidic^[77] or basic^[78] conditions as depicted in Figure 25.

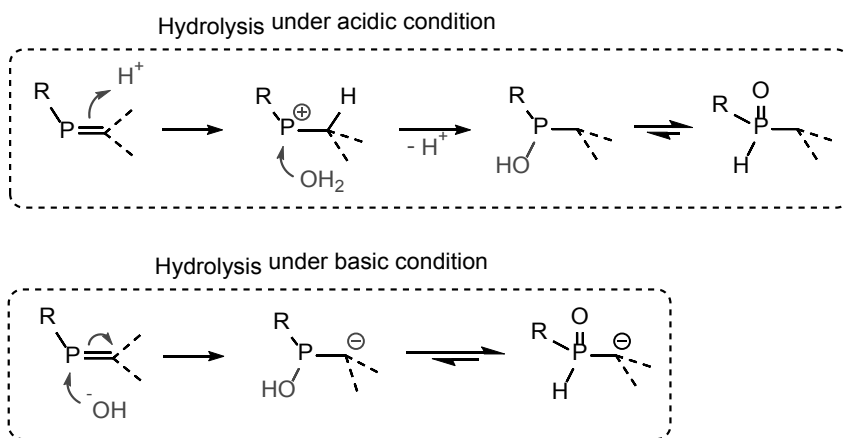
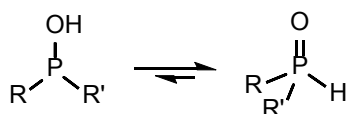


Figure 25. Hydrolysis of phosphalkenes under acidic (top) and basic (bottom) conditions

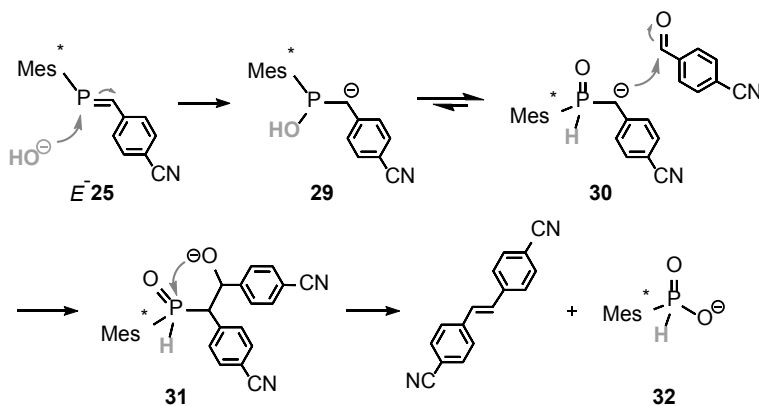
Hydrolysis of phosphalkenes encompasses tautomerization of phosphinous acids to their corresponding SPOs. The latter exist as a mixture of P(III) and P(V) isomers although the P(V) isomer is air-stable and predominant under ambient conditions.^[79] (Scheme 38)



Scheme 38. Tautomerization between P(III)-bearing phosphinous acid and secondary phosphine oxide with P(V) center

4.3. Mechanistic Investigations on the Unexpected Side-reaction

As previously mentioned in Chapter 4 (p. 55), an unexpected olefinic side-product in the *phospha*-HWE reaction attracted our attention to an extent that we focused our investigation on finding the mechanism that would explain its formation. The hypothesis was that the olefin is formed from the phosphalkene product under the reaction or work-up conditions. Considering the electrophilic nature of the P=C bond of phosphalkenes, a nucleophilic attack at the P-center was anticipated. With trapping of phosphalkenes in mind, we hypothesized that similar type of P=C “activation” would have played a key role in forming the stilbene side-product. We hypothesized that the reaction of a hydroxide nucleophile with the phosphalkene should lead to the corresponding phosphinous acid **29** which is in tautomerization with its secondary phosphine oxide tautomer **30**. The secondary phosphine oxide has a close resemblance to the classical HWE reagent and should, in theory, be capable of transforming the carbonyl compounds to olefins. In this way, Mes^{*}-bearing phosphinate **32** would be the final by-product of the reaction. (Scheme 39)



Scheme 39. Our proposed final mechanism for alkene formation. Hydroxide attack at P=C followed by a tautomerization to the corresponding SPO carbanion **30** conducts the sequence to the alkene formation.

To investigate the validity of the hypothesis, we monitored our suggested reaction sequence by ^{31}P NMR spectroscopy. The addition of neat water does not lead to any reaction due to the high kinetic stability of the phosphalkene (Figure 26, b). Thus, the sequence was started by the addition of sodium hydroxide to pure phosphalkene *E*-**25** in wet THF. The reaction was slow but full consumption of the phosphalkene was achieved after 2-3 days and a new peak at 25 ppm assigned to SPO **30** appeared in the ^{31}P NMR spectrum (Figure 26, b→c→d). Addition of 4-cyanobenzaldehyde at this point consumes most of the SPO overnight and gives rise to by-product **32** at 15 ppm (Figure 26, d→e), along with the formation of the alkene product in high yields.

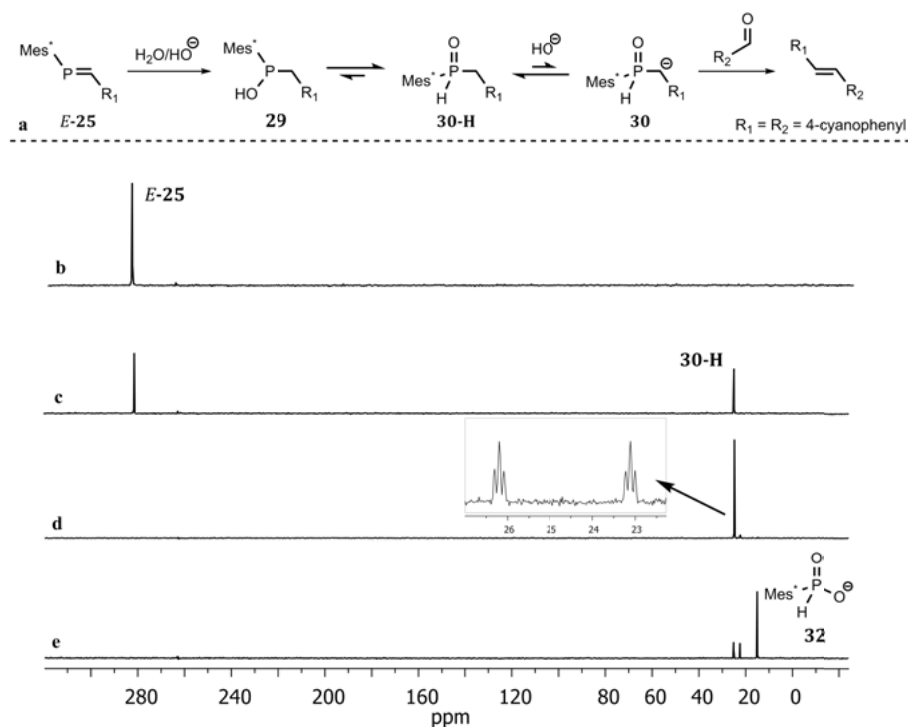


Figure 26. ^{31}P NMR monitoring of the reaction from consumption of phosphalkene to formation of the phosphinate by-product

Two equilibria are assumed to be present in the proposed reaction (Figure 26, a). The first equilibrium is the tautomerism between phosphinuous acid **29** and SPO **30**.^[80] This equilibrium lies largely on the more stable SPO under ambient conditions as no sign of phosphinuous acid was ever observed by ^{31}P NMR. The second equilibrium is an acid/base equilibrium between SPO **30-H** and its deprotonated form. The proton-coupled ^{31}P NMR (C_6D_6) spectrum revealed that the peak at 25 ppm is actually a doublet of triplets with $^1J_{\text{PH}} = 498$ Hz and $^2J_{\text{PH}} = 17$ Hz, which corresponds to the SPO **30-H** (Figure 26, d).

These J values and chemical shift are very similar to those of Mes^{*}P(O)HCH₂Ph (CDCl₃, $\delta_P = 28$ ppm, $^1J_{PH} = 495$ Hz and $^2J_{PH} = 15$ Hz) reported by Yoshifuji and colleagues.^[81] Such a splitting pattern indicates that SPO **30-H** is the predominant species, rather than the deprotonated species **30**. However, as soon as 4-cyanobenzaldehyde is added to the reaction, SPO **30** is slowly consumed and drives the reaction forward until its full consumption (Figure 26, d→e). Identification of SPO **30-H** also confirms its role as an intermediate in the reaction.

After the aqueous work-up, 2,4,6-tri-*t*-butylphenyl phosphinic acid **32-H** was isolated, as a pure colorless solid. Isolation of this by-product further supports the accuracy of our hypothesis regarding the reaction sequence and the ionic mechanism that is postulated. The proton-coupled ³¹P NMR spectrum of phosphinic acid **32-H** (CDCl₃) shows a doublet at 27 ppm with a coupling constant of $^1J_{PH} = 571$ Hz. The same coupling constant was also observed in the ¹H NMR spectrum of the compound, with an extremely large doublet at 8.16 ppm.

Finding the Best OH-Source

In the sequence described above, hydrolysis of the phosphalkene by sodium hydroxide seems to be the lowest step of the reaction. The low solubility of NaOH in THF (*i.e.* solvent of the reaction) could be the main reason for this poor performance and it was therefore decided to test different sources of hydroxide to shorten the reaction times. (Table 3)

Table 3. Sources of hydroxide and different reaction times for the conversion of phosphalkene *E*-**25** to SPO **30**

| Base | Full P=C Consumption |
|--|----------------------|
| NaOH/H ₂ O | 2 days |
| KOH/H ₂ O | 2 days |
| CsCO ₃ /H ₂ O | no reaction |
| CsOH/H ₂ O | Overnight |
| KOH/18-crown-6 | Overnight |
| Bu₄NOH_(aq.) 40% | Immediate! |

Changing the nucleophile from NaOH to KOH did not lead to significant improvements. CsCO₃ in wet THF did not react with the phosphalkene at

all, while a CsOH/H₂O system improved the reaction time to overnight. The larger size of the counter cation in this case may be the main reason for the improved solubility and reduced reaction time. Water-free conditions were also tested by the addition of KOH/18-crown-6 to THF solution of the phosphalkene. The result however was not satisfactory and the reaction time did not improve significantly.

The picture changed dramatically when tetrabutylammonium hydroxide (TBAOH) was tested for the conversion of the phosphalkene. Upon addition, an immediate color change is observed and the reaction is complete within seconds. TBAOH is inexpensive and commercially available as a 40% aqueous solution. In the presence of an aldehyde, the whole reaction is complete within seconds and a peak at 12 ppm appears in the ³¹P NMR spectrum, corresponding to the Mes^{*}-phosphinate **32** as shown in Figure 27. This chemical shift is 4 ppm upfield compared to the experiment with NaOH, a difference that is most likely an effect of the different counter cation that forms an ion pair in THF solution.

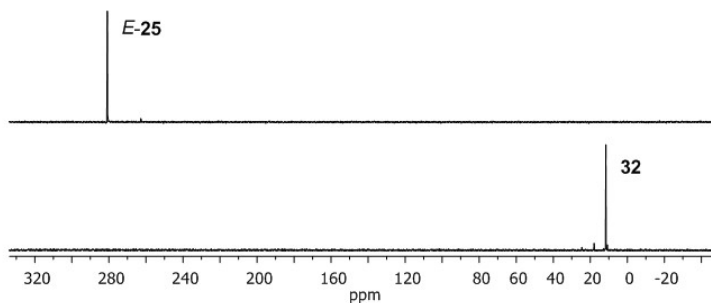
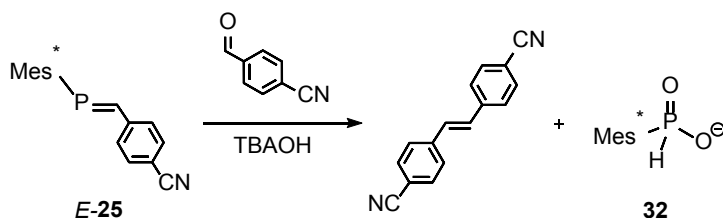
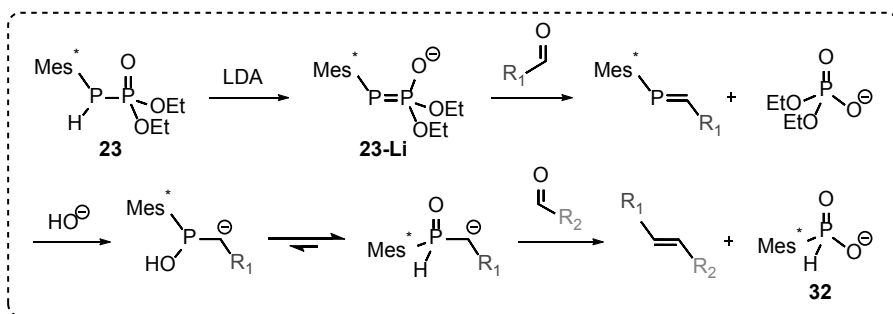


Figure 27. ³¹P NMR monitoring for the reaction of TBAOH with *E*-**25** in the presence of 4-cyanobenzaldehyde. This reaction forms the corresponding SPO **30** which readily reacts with 4-cyanobenzaldehyde to produce the final alkene and phosphinate **32**.

4.4. Shaping a One-pot Reaction

With the modified procedure for the *phospha*-HWE described in section 4.5, phosphoalkenes are formed within minutes. It was also shown that phosphoalkene *E*-**25** can undergo hydrolysis and a subsequent HWE-type reaction with 4-cyanobenzaldehyde to afford alkene NPhC=CPhCN within few minutes. With the two reactions in hand, the time was ripe to shape a one-pot reaction that would reductively couple two aldehydes (Scheme 40).

In this manner, we aimed for the synthesis of *E*-**25** via a *phospha*-HWE reaction, followed by its hydrolysis *in situ*. The hydrolyzed species *i.e.* the corresponding SPO is expected to react with 4-cyanobenzaldehyde to furnish the alkene product. Hence, phosphoalkene *E*-**25** would be an intermediate in the one-pot reaction.



Scheme 40. General representation of the one-pot reaction. In our mechanistic studies: $R_1 = R_2 = 4$ -cyanophenyl

^{31}P NMR monitoring was the tool to follow the whole sequence of our one-pot reaction (Figure 28). Transformation of the two doublets of **23** at -90 and 34 ppm into a new set of doublets of **23-Li** at -119 and 69 ppm could be observed equally well as the conversion of the latter to *E*-**25** (resonance at 284 ppm) and diethyl phosphate (resonance at 1 ppm). TBAOH_(aq) and a second equivalent of benzaldehyde was added to *E*-**25** at this point which resulted in full consumption of *E*-**25** and the appearance of a new peak at 12 ppm that is assigned to the Mes^{*}-phosphinate **32**. The desired alkene final product was isolated in high yields proving the viability of our one-pot reaction. Noteworthy are the beautifully clean NMR spectra that suggest very high conversions in each of the steps.

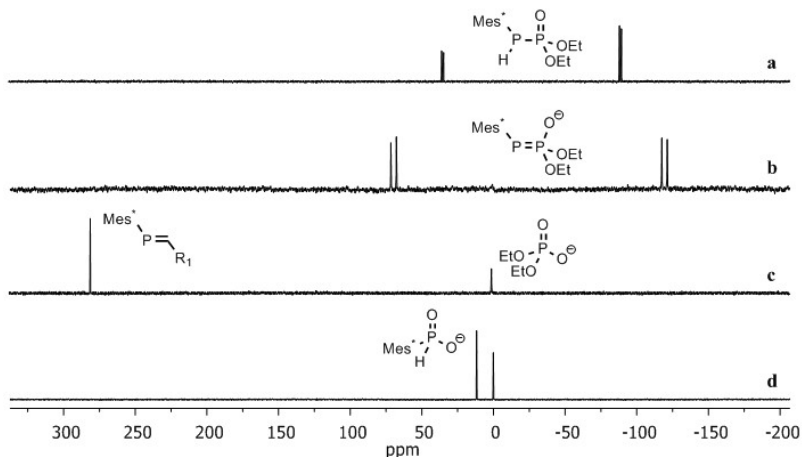


Figure 28. Following the one-pot sequence by ^{31}P NMR. (*a*→*b*): lithiation of **23** to **23-Li**. (*b*→*c*): phospho-HWE reaction of **23-Li** with 4-cyanobenzaldehyde and formation of *E*-**25** and diethyl phosphate. (*c*→*d*): reaction of TBAO H with *E*-**25** and subsequent reaction of the resulted SPO with second equivalent of 4-cyanobenzaldehyde to give the alkene product and Mes^* -phosphinate by-product **32**. The signal at 1 ppm increases in intensity (d) which is probably due to its enhanced solubility after adding the aqueous solution of TBAOH to the THF solution of the reaction.

It is interesting to note that adding both equivalents of 4-cyanobenzaldehyde to **23-Li** in the beginning of the sequence gives the same outcome and consequently provides a more simplified practical procedure. It thus seems that the second equivalent of aldehyde is intact until it reacts with the deprotonated SPO **30** as soon as the latter is formed in the reaction environment.

4.5. Substrate Scope

So far, we have introduced a novel procedure to make *E*-4,4'-(ethene-1,2-diyl)dibenzonitrile in a mild and effective way. With the optimized reaction conditions, the scope of the newly developed procedure was evaluated. The studies were divided into two parts: first, the homocoupling of aldehydes to symmetrical *E*-alkenes, and second, the synthesis of unsymmetrical *E*-alkenes from two different aldehydes.

4.5.1. Homocoupling of Aldehydes to Symmetrical *E*-Alkenes

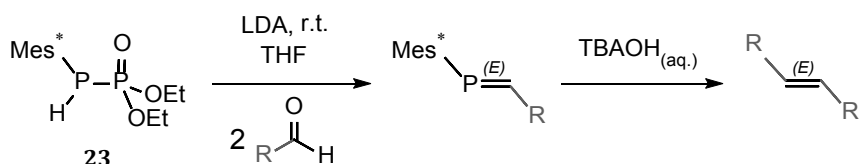


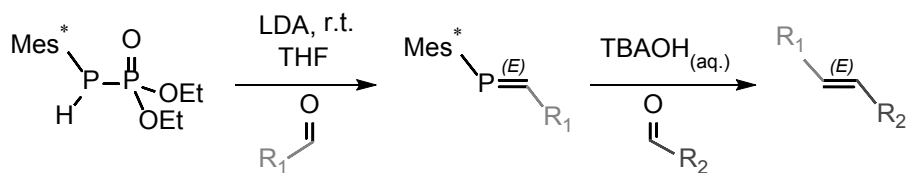
Table 4 shows the results of the homocoupling of a series of aldehydes. Two equivalents of benzaldehyde were reacted with enolate **23-Li** in order to synthesize stilbene. A peak at 258 ppm in the ^{31}P NMR confirmed the formation of $\text{Mes}^*\text{P}=\text{C}(\text{Ph})\text{H}$. $\text{TBAOH}_{(\text{aq})}$ was added at this point which consumed the phosphalkene in about 45 minutes and stilbene was eventually obtained in 37% isolated yield. Although this yield is only moderate compared to what the McMurry coupling affords for benzaldehyde homocoupling (97%), two important points can already be concluded: First, this reaction is the first example of reductive aldehyde homocoupling which is conducted under an ionic mechanism and at room temperature. Second, consumption of the $\text{Mes}^*\text{P}=\text{C}(\text{Ph})\text{H}$ was achieved in a reasonably short time, but still longer compared to that of *E*-**25**. This is most likely because of the higher electron-deficiency in the latter and the fact that electron-poor systems perform better in the HWE-type reaction. Hence, we tried the reaction with electron-deficient aldehydes such as 4-bromobenzaldehyde. High conversion of 82% to the corresponding alkene was achieved. This result also shows that the presence of halides on the molecule is tolerated in our coupling method. Heterocyclic 6-bromo-2-pyridinecarboxaldehyde was the next aldehyde tested which afforded the homocoupling product also with a high conversion (80%).

Table 4. Homocoupling of aldehydes to *E*-alkene products.

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

Homocoupling of electron-rich trimethylacetaldehyde did not occur at all. The P=C bond of Mes^{*}P=C(*t*-Bu)H is completely stable towards the addition of TBAOH_(aq), and the reaction was thus stalled at this stage. The lack of reactivity may be a result of steric rather than electronic effects. Considering this possibility, hydroxide, perhaps ion-paired to the bulky tetrabutylammonium, may not be able to reach the P-atom in phosphalkene Mes^{*}P=C(*t*-Bu)H which itself is sterically crowded with a large *t*-butyl and Mes^{*} groups.

4.5.2. Unprecedented Reductive Coupling of Two Different Aldehydes to Unsymmetrical *E*-alkenes

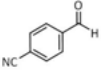
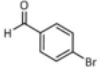
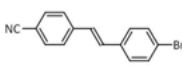
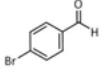

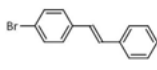
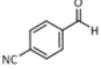

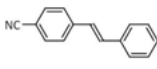
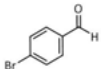
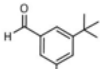
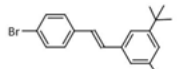
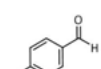
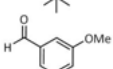
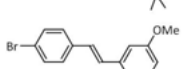


The most important feature of our developed procedure is the selective reductive coupling of two *different* aldehydes to unsymmetrical *E*-alkenes. This is a vast improvement compared to the McMurry coupling which gives a statistical mixture of *E*-alkenes: the desired unsymmetrical product and two symmetrical *E*-alkenes.

We tested our method on a diverse selection of aldehydes (Tables 5-7). Since electron-deficient systems proved to give better conversions, we used NCPHCHO, BrPhCHO and the pyridine-based aldehydes for the first part of the sequence *i.e.* the phospho-HWE reaction. Corresponding phosphalkenes were formed in full conversions and used *in situ* for the next step, *i.e.* the reaction with TBAOH and the second aldehyde. The overall result was quite satisfactory as good conversions to unsymmetrical *E*-alkenes were observed in some cases. In all experiments described hereafter, no trace of the symmetrical *E*-alkenes or any *Z*-alkenes were detected.

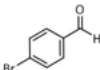
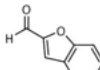
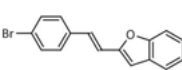
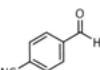
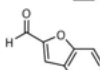
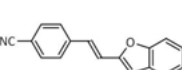
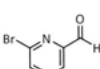

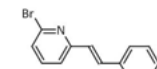
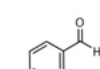
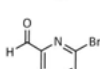
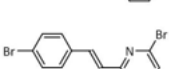
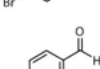

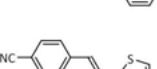
Excellent conversion of 91% was obtained when electron-deficient BrPhCHO and 4-NCPHCHO were coupled (Table 5, Entry 1). Benzaldehyde was then coupled as the second aldehyde to 4-BrPhCHO and 4-NCPHCHO giving good conversions of 56 and 57%, respectively (Table 5, Entries 2-3). Benzaldehyde derivatives with substituents in the *meta* positions like 3,5-di-*t*-butylbenzaldehyde bearing two bulky electron-donating *t*-Bu groups and 3,5-dimethoxybenzaldehyde showed high conversions of 58% and 74%, respectively (Table 5, Entries 4-5). In the latter example, the methoxy groups at the *meta*-position cannot contribute to resonance and therefore are unable to push electron density into the system. At the same time, their electron-pulling inductive effect make the system electron-deficient which may explain the high conversion with 3,5-dimethoxybenzaldehyde.

Table 5. Reductive cross coupling of different benzaldehydes to unsymmetrical *E*-alkene products

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

The next compounds that were tested for the second part of the reaction were heterocyclic aldehydes including benzofuran-, pyridine-, and thiophene-based systems (Table 6). These aldehydes give moderate to good conversions to their corresponding alkene products.

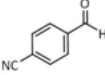

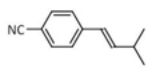
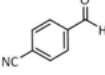

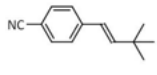
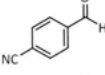

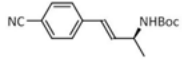
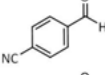

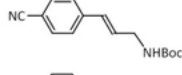
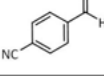
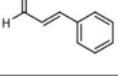
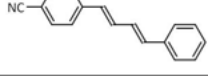
Table 6. Reductive cross coupling of heterocyclic aldehydes and benzaldehydes to their corresponding *E*-alkenes

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

Best results were obtained with 2-benzofurancarboxaldehyde which gives 50% and 68% conversions when added to 4-BrPhCHO and 4-NCPHCHO respectively (Table 6, Entries 1-2). 6-Bromo-2-pyridinecarboxaldehyde led to the corresponding *E*-alkenes as well, although with lower conversions especially when coupled as the second aldehyde to benzaldehyde (Table 6, Entries 3-4). Coupling of 2-thiophenecarboxaldehyde was also successful indicating that the method is applicable to thiophenes as well (Table 6, Entry 5).

In the next experiments, four aliphatic substrates were chosen to couple with 4-cyanobenzaldehyde (Table 7). A surprisingly good conversion of 60% was obtained with *iso*-butyraldehyde (Table 7, Entry 1). As expected, the other three electron-donating systems afford the alkenes in lower yields. The reaction with trimethylacetaldehyde gives 27% conversion (Table 7, Entry 2) which may be due to the bulkiness of the *t*-Bu group. NHBoc-bearing aldehydes gave low conversions of 24% and 10% (Table 7, Entries 3-4). Although relatively low, these yields are still valuable considering the functional group tolerance and the presence of an acidic α -proton which can promote competitive aldol reaction under the basic conditions of the reaction. Considering this fact, the 60% conversion with *iso*-butyraldehyde is specifically remarkable.

Table 7. Reductive cross coupling of 4-cyanobenzaldehyde with aliphatic and vinylic systems

| Entry | 1 st Aldehyde | 2 nd Aldehyde | Product | Conversion [%] (isolated yield) |
|-------|---|---|---|------------------------------------|
| 1 |  |  |  | 60 |
| 2 |  |  |  | 27 |
| 3 |  |  |  | 24 |
| 4 |  |  |  | 10 |
| 5 |  |  |  | 37 |

The final substrate that was selected to couple with 4-cyanobenzaldehyde was *trans*-cinnamaldehyde. A moderate 37% yield (Table 7, Entry 5) demonstrates that our method is also applicable to vinylic systems despite

the electron-donating nature of this moiety and its reactivity that is associated with the α,β -unsaturation.

4.6. Advantages over McMurry Reaction

Both the McMurry coupling and the method described herein reductively couple two aldehydes to the corresponding alkene products. Notably, the methodology that we developed has some advantageous features over the McMurry coupling which we outline here.

Our reaction is carried out by a phosphanylphosphonate reagent which is easily prepared on a multi-gram scale without the presence of any metal. Consequently, the whole reaction is transition metal-free. This differs from the McMurry coupling which uses low-valent Ti reagents that are prepared *in situ* from TiCl_4 and reducing agents such as Zn or Zn(Cu). Unlike the McMurry coupling which typically requires high temperatures and long reaction times, all transformations in our coupling are carried out at room temperature within a few minutes. From a stereo-chemical point of view, our coupling method produces *E*-alkenes in all cases with no observable sign of the *Z*-alkene isomer. The McMurry coupling generally produces an *E/Z* mixture although the *E*-isomer is predominant.^[74a]

Most remarkably, our coupling reaction benefits from an ionic mechanism in which two *different* aldehydes can cross-couple in a controlled manner to afford the *E*-alkene product selectively. No trace of homo-coupled alkene was ever observed. This selectivity is a vast improvement compared to the McMurry coupling, the radical mechanism of which does not allow a selective alkene formation from two different aldehydes. Instead, a statistical mixture of products is obtained.^[82]

4.7. Limitations of the Reductive Aldehyde Coupling Method

Like the majority of reactions in organic chemistry, also this methodology described above suffers from some intrinsic drawbacks. Knowing these limitations gives us more insight into the chemistry of the reaction which can help us to improve the method in the future. Some possible limitations of our coupling reaction are described herein.

Our new coupling method occurs via a change in polarity (Umpolung) of a carbon center. In this manner, the polarity of the carbon is changed from δ^+ on the first aldehyde to δ^- on the phosphalkene. This effect leaves the P-center with a partial positive charge and makes the P=C bond electrophilic. Nucleophilic attack of hydroxide at the P-center in the next step activates the

P=C bond and enhances the nucleophilicity of its C-center. These two factors, the electrophilicity of the P-center in the phosphalkene and the nucleophilicity of the C-center on the secondary phosphine oxide, define the limitations in terms of substrate scope in our coupling reaction. (Figure 29)

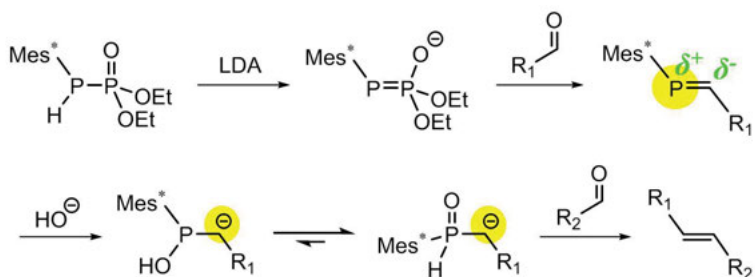
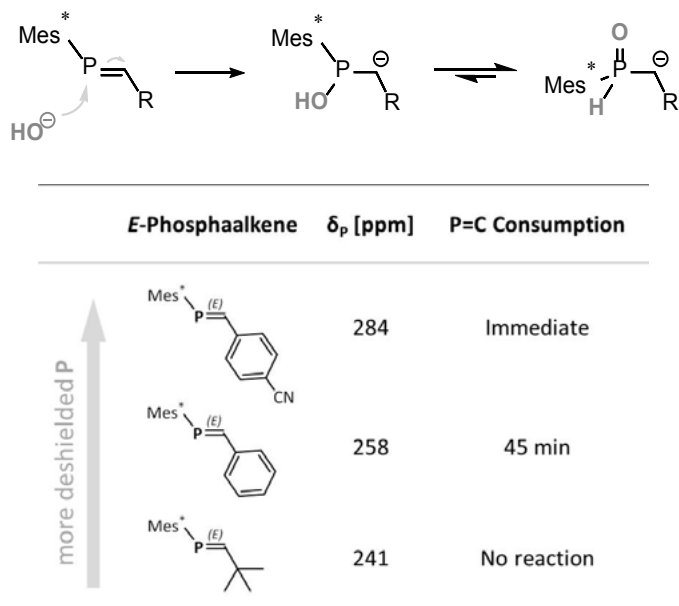


Figure 29. Outcome of the reaction is strongly dependent on two factors: reactivity of P=C against the nucleophilic hydroxide and nucleophilicity of SPO carbanion

Phosphaalkenes with electron-withdrawing groups such as 4-cyanophenyl, 4-bromophenyl, and pyridinyl on their P=C seem to be stronger electrophiles and engage in facile hydrolysis within a few minutes after the addition TBAOH_(aq). Conversely, phosphalkene Mes*P=C(*Ph*)H shows a decreased reactivity against the nucleophilic hydroxide and is consumed only after 45 min. Final conversions obtained with this phosphalkene were clearly lower than those bearing electron-withdrawing groups. Phosphaalkene Mes*P=C(*t-Bu*)H was the most extreme case, being completely stable against hydroxide addition even after days. As a result, the reaction sequence is stalled at this stage and no further reactivity with a second aldehyde is observed.

Interestingly, a correlation between the phosphalkene chemical shifts and their reactivity towards hydroxide was observed (Table 8). A more deshielded P-atom in phosphalkenes with downfield chemical shifts (*i.e.* with EWGs) seems to be a better electrophile as it reacts extremely fast with the hydroxide. A clear example is *E*-**25** with δ_p of 284 ppm that reacts immediately. In contrast, the more shielded phosphorus center in phosphalkene Mes*P=C(*t-Bu*)H with upfield chemical shift of 242 ppm is basically unreactive towards hydroxide addition. Mes*P=C(*Ph*)H with a ³¹P NMR chemical shift of 258 ppm is in an intermediate range and its reaction with hydroxide proceeds slower. However, it is too early to draw a clear conclusion from these observations and a true correlation between δ_p of phosphalkenes and their electrophilicity requires more data points.

Table 8. Different electrophilic behavior of phosphalkenes against hydroxide attack



Because the last step of our coupling method is an HWE-like reaction, it suffers from similar type of limitations as the HWE reaction itself. Hence, the nucleophilicity of the carbon center in the SPO is another parameter that limits the substrate scope (Figure 30). Best results are obtained with more stabilized carbanions as expected. For example, the best conversions were generally obtained with 4-cyanophenyl on the SPO.

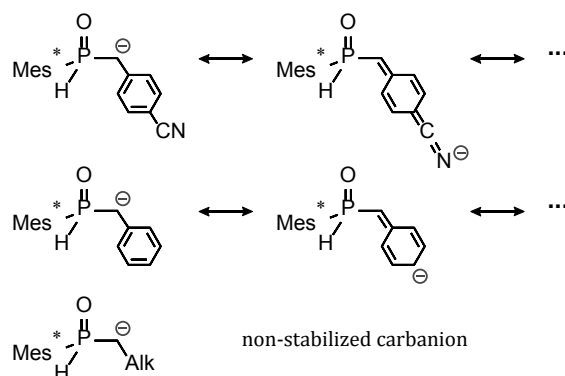


Figure 30. Nucleophilicity of the SPO in different systems. The SPO carbanions with anion stabilizing groups show stronger nucleophilicity in the reaction

The negative charge on the C-atom is highly stabilized in this case due to resonance with the electron-withdrawing 4-cyanophenyl moiety. Resonance stabilization is also possible in the absence of the cyano substituent at the phenyl group, albeit less effective. Such stabilization is not possible when the SPO contains a *t*-Bu on the α -carbon since the *t*-Bu group is electron-pushing and provides no stabilization either via inductive effect or resonance.

In general, non-stabilized phosphonates bearing aliphatic groups on the α -carbon do not seem to drive the reaction towards alkene products. However, a modification of HWE reaction was introduced in 2003 in which non-stabilized β -hydroxy phosphonates could react with carbonyl compounds and give the alkene products via saponification of the phosphonate followed by a subsequent addition of diisopropylcarbodiimide (DIC).^[83] Such modification is also worth exploring in our case with the hope of improving the substrate scope and allowing the reaction of aliphatic aldehydes as the first coupling partner.

4.8. Outlook

The reductive aldehyde coupling to alkenes presented herein is a method that leaves much room for future explorations. Although our coupling method already performs at an acceptable level, it is anticipated that the procedure can be further modified and improved to become a versatile tool in organic chemistry for the preparation of C=C bond containing compounds.

The scope of our coupling method is somewhat limited, in particular when it comes to electron-rich aldehydes. Also ketones which would be a natural extension of the presented work cannot be coupled under the currently employed conditions, using phosphanylphosphonates as reagents. Future studies will strongly focus on overcoming these shortcomings to extend the substrate scope of the reaction further.

The substrate scope of the reductive coupling would most likely increase if one or more of the following factors could be improved:

- Electrophilicity of the P=C bond in phosphalkene
- Acidity of the α -proton in SPO
- Nucleophilicity of α -carbon in deprotonated SPO (or generally an HWE-like P=O-containing intermediate)

The phosphalkene *intermediate* in our coupling method was formed via a phospho-HWE reaction. However, there are numerous synthetic procedures in the literature that lead to phosphalkenes, and any of these methods could potentially be used as an alternative to the phospho-HWE reaction to execute the first step of our two-step one-pot coupling reaction. The protecting group on the phosphalkene is another parameter than can be manipulated. Besides Mes*, alternative protecting groups at the phosphorus center

could be incorporated to investigate their steric or electronic effects. It is intuitive to assume that such manipulations will impact the reactivity of the different intermediates in the coupling.

So far, we have only used hydroxide as the nucleophilic partner to activate the P=C bond of phosphalkene. The nucleophile is another component that can be altered for further explorations. For example, organolithium (e.g. BuLi) or Grignard (e.g. EtMgBr) reagents can be used as alternative nucleophiles. Nucleophilic attack of BuLi (and MeLi) on phosphalkenes have previously been reported by Gates *et al* and even followed by an oxidation step to give a phosphine oxide species^[76] that closely resembles the phosphinite or SPO systems that we employed.

The secondary phosphine oxide (SPO) derived from the phosphalkene is another intermediate in the sequence that leads to coupling to the final alkene product. There are however alternative synthetic pathways to SPOs in the literature^[84] which might eliminate the necessity of phosphalkene synthesis in the first place.

Finally, a main drawback of our method is the P=O-containing waste that is produced at the end of the coupling process. One suggestion for removal of this by-product is the oxalyl chloride treatment that was reported by Gilheany and colleagues for removing by-products in the Wittig reaction. A similar reaction outcome is obtained in our coupling method: an alkene product and a P=O-containing by-product. Therefore, addition of oxalyl chloride could allow the removal of the P=O-containing waste by a simple filtration and leave the alkene pure and intact. However, the ultimate goal for this project is a catalytic reaction with a recycled waste, in which two carbonyl compounds are either homo- or cross-coupled. Inspired by the catalytic Wittig^[85] and Appel^[86] reactions, such a goal should not be impossible to achieve!

5. Concluding Remarks and Summary

We were successful in utilizing the bulky Dmp group in the synthesis and isolation of a new series of *C,C*-dibromophosphaalkenes. These phosphalkenes are invaluable precursors for post-synthetic purposes owing to their $\text{P}=\text{C}(\text{Br})_2$ termini. NMR studies showed that the *C,C*-dibromophosphaalkenes similarly feature a rotational hindrance which is due to the steric clash of their $-\text{P}=\text{CBr}_2$ moiety with the mesityl wings of the Dmp group. UV/Vis spectra of these phosphalkenes show that the most conjugated phosphalkene absorbs at higher λ_{max} while cyclic voltammograms indicate that the reductions proceed mostly on the π -conjugated parts of the molecules. These results are in agreement with the fact that the more π -conjugated systems have smaller HOMO-LUMO gaps.

In addition to the *C,C*-dibromophosphaalkenes, we were also able to synthesize two new diphosphenes using the Dmp-containing starting materials. In the case of the bis(diphosphene) compound, the isolation failed due to a possible decomposition although the synthesis itself was successful.

Moreover, we developed a new method for the sequential alkynylation of phosphalkenes with full control over the stereochemistry of the alkynylated products. This method is in fact the phosphorus version of the alkynylation of alkenes which uses similar sulfonylacetylene reagents for transferring the acetylenic moiety. This method proved to be applicable not only to the Mes^* -protected phosphalkenes but also the Dmp-stabilized phosphalkenes.

We developed two more methodologies in which organophosphorus compounds are at the core of the chemistry. First, we introduced a novel approach to make $\text{P}=\text{C}$ bonds from aldehydes using an organophosphorus reagent, *i.e.* the metal-free phospho-HWE reaction. Second and more importantly, we discovered a new coupling method that allows the preparation of alkenes from aldehydes. The main achievements in chapters 4 and 5 are summarized as follows:

- ✓ We were able to synthesize and isolate the first metal-free phosphanylphosphonate and structurally characterize it. The molecule is stabilized without the need for coordination to a metal fragment as it carries a Mes^* protecting group on the P(III) center.
- ✓ The phosphanylphosphonate can be prepared on a multi-gram scale in good overall yields. If stored dry and under inert gas in the freezer, it can survive for long periods of time without any sign of decomposition.

- ✓ We could successfully use this phosphanylphosphonate as a reagent in a transition metal-free phospho-HWE reaction which benefits from mild conditions and very short reaction times.
- ✓ The phospho-HWE reaction proved to have a broad substrate scope as aliphatic, aromatic, heterocyclic, and vinylic aldehydes can be converted to their corresponding metal-free phosphoalkenes.
- ✓ Phosphoalkene, obtained from the phospho-HWE reaction, could be activated at the P=C bond and reacted further with an aldehyde to form alkenes.
- ✓ A two-step, one-pot reaction was developed which uses Mes^{*}-stabilized phosphanylphosphonate as a reagent to convert an aldehyde to the corresponding phosphoalkene. The latter reacts with TBAOH to give an SPO which can react with a second aldehyde to the corresponding alkene product. With these findings, a substrate scope for the homocoupling of aldehydes to symmetrical *E*-alkene products was investigated.
- ✓ The one-pot reaction is an example of Umpolung as the polarity of the carbon center is changed from δ^+ in the aldehyde to δ^- in the phosphoalkene. Contrary to the McMurry coupling with its radical mechanism, our reaction takes place via a step-wise ionic mechanism. An ionic mechanism allows for the selective formation of unsymmetrical *E*-alkenes from two different aldehydes, thereby avoiding a statistical product mixture as observed in the McMurry coupling. A substrate scope for the selective synthesis of unsymmetrical *E*-alkenes was explored and the validity of our mechanistic model confirmed.
- ✓ Our coupling method benefits from mild conditions such as ambient temperatures and short reaction times and generally provides good yields with high stereoselectivity towards *E*-alkenes.

Svensk sammanfattning

Vetenskapens och teknikens värld har utvecklats i hastig takt under de senaste decennierna och den otaliga mängd uppfinningar som utvecklats inom olika forskningsområden bidrar till en ständig förändring av den värld vi lever i. Ett av de områden som har fått störst uppmärksamhet är kemiområdet, där ett stort antal upptäckter och förbättringar har gjorts. Bland dessa kan nämnas progressiv utveckling och tillämpning inom katalys, elektronik, miljö- och energirelaterade områden o.s.v. Denna avhandling ägnas huvudsakligen åt den nya utvecklingen inom *organisk fosforkemi*. Nya organiska fosforföreningar har tagits fram dels för potentiell användning inom elektronik samt materialvetenskap, dels för att användas som reagens inom organisk syntes.

Organiska fosforföreningar som enskilda molekyler eller inkorporerade i organisk elektronik (t.ex. lysdioder, halvledare, fotovoltaiska celler o.s.v.) har fått ökad uppmärksamhet under de tre senaste årtiondena. Närvaron av fosfor stör de elektroniska egenskaperna hos de π -konjugerade systemen och tillhandahåller även möjligheter för efterföljande syntetiska modifieringar. När fosfor byggs in i ett π -konjugerat kolskelett minskar energiskillnaden mellan systemets HOMO och LUMO. Detta öppnar upp för intressanta elektroniska egenskaper såsom möjligheten att justera systemets bandgap. Att syntetisera nya π -konjugerade organiska fosforföreningar med potentiell tillämpning inom organisk elektronik är därför av stort intresse. Avhandlingens första del ägnas åt syntesen av ett startmaterial som möjliggör en mängd olika syntesvägar för lågvalenta fosforföreningar (även andra huvudgruppsämnen såsom As, Bi, Si, o.s.v.). Detta startmaterial användes för att framställa nya fosfaalkener samt difosfener. En rad nya *C,C*-dibromfosfaalkener, som i sig utgör intressanta startmaterial för framställningen av mer sofistikerade π -konjugerade system, syntetiserades. NMR- och UV/Vis-spektroskopi samt CV användes för att studera de framställda fosfaalkenernas spektroskopiska och elektroniska egenskaper. I NMR spektra av fosfaalkenerna observerades s.k. linjebreddningar, vilka tyder på rotationshinder i molekylernas respektive strukturer. Denna typ av linjebreddning uppstår när molekylens $-P=CBr_2$ -del kolliderar med Dmp-gruppens mesitylringar. Spektra från UV/Vis-mätningar visade att den mest konjugerade fosfaalkenen absorberar vid högre λ_{max} , medan CV-mätningar indikerade att reduktion sker, framförallt, i de π -konjugerade delarna av molekylerna. Dessa resultat överensstämmer med det faktum att mer π -konjugerade system har mindre bandgap.

Utöver *C,C*-dibromfosfaalkenerna, framställdes även två nya difosfener, vilket påvisar startmaterialets användbarhet.

Upptäckten av nya syntesmetoder samt reaktioner är en viktig komponent för utveckling inom organisk kemi och i den här avhandlingen presenteras nya syntesvägar för organiska fosforföreningar. Ett annat viktigt användningsområde för organiska fosforföreningar, är som reagens i organisk kemi. Wittig-reaktionen, som gav Georg Wittig Nobelpriset i kemi 1979, är ett tydligt exempel på den typen av användning där fosfoniumylider nyttjas som reagens för att omvandla karbonylföreningar till alkener som är viktiga för organisk syntes samt industriell organisk kemi. I denna avhandling presenteras en fosforversion av Wittig-reaktionen, d.v.s. fosfa-HWE, vilken ger *fosfaalkener* som produkt. En metallfri fosfanylfosfonat används som reagens för att omvandla aldehyder till motsvarande fosfaalkener. Metoden har ett brett substratomfång och omvandlar en rad olika aldehyder såsom alifatiska, aromatiska, heterocykliska samt vinylliska system till motsvarande fosfaalkenprodukter. Andra fördelar med reaktionen är att den sker under milda förhållanden, ger god omvandling samt har hög *E*-stereoselektivitet.

Betydelsen av alkener och deras tillämpningar i våra liv är otvivelaktig. Att ta fram nya och innovativa reaktioner för bildandet av C=C-bindningar är således av stor betydelse inom organisk kemi. I den sista delen av avhandlingen presenteras en ny metod för reduktiv koppling av aldehyder till olefiner. Denna enkärnsreaktion, vilken har stora fördelar relativt McMurry-kopplingen, möjliggör selektiv syntes av symmetriska såväl som osymmetriska *E*-alkener. Den ovannämnda fosfanylfosfonaten agerar reagens vid kopplingen av aldehyderna med en fosfaalken som mellanprodukt. Mekaniskt omvandlas en aldehyd till motsvarande fosfaalken genom en fosfa-HWE-reaktion. Fosfaalkenen aktiveras sedan med en hydroxidnukleofil, vilket ger en sekundär fosfinoxid (SPO) vid tautomerisering av den erhållna fosfinsyran. SPO reagerar sedan med den andra aldehyden och bildar alkenprodukten. Denna reaktion är ett exempel på Umpolung där polariteten hos kolcentret går, från δ^+ i aldehyden, till δ^- i fosfaalkenen. Den aldehydreduktiva kopplingsreaktionen kan genomföras under milda förhållanden och ger god omvandling samt hög *E*-stereoselektivitet.

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