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### Tandem-, Domino- and One-Pot Reactions Involving Wittig- and Horner-Wadsworth-Emmons Olefination

Fatima Merza, Ahmed Taha and Thies Thiemann

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#### Abstract

The Wittig olefination utilizing phosphoranes and the related Horner-Wadsworth-Emmons (HWE) reaction using phosphonates transform aldehydes and ketones into substituted alkenes. Because of the versatility of the reactions and the compatibility of many functional groups towards the transformations, both Wittig olefination and HWE reactions are a mainstay in the arsenal of organic synthesis. Here, an overview is given on Wittig- and Horner-Wadsworth-Emmons (HWE) reactions run in combination with other transformations in one-pot procedures. The focus lies on one-pot oxidation Wittig/HWE protocols, Wittig/HWE olefinations run in concert with metal catalyzed cross-coupling reactions, Domino Wittig/HWE—cycloaddition and Wittig-Michael transformations.

**Keywords:** Wittig olefination, one-pot reactions, Domino reactions, tandem reactions, Horner-Wadsworth-Emmons olefination

#### 1. Introduction

The Wittig olefination utilizing phosphoranes and the related Horner-Wadsworth-Emmons (HWE) reaction using phosphonates transform aldehydes and ketones into substituted alkenes. Because of the versatility of the reactions and the compatibility of many functional groups in the transformations, both Wittig olefination and HWE reactions are a mainstay in the arsenal of organic synthesis. The mechanism of the Wittig olefination has been the subject of intense debate [1]. While initially it was supposed that all Wittig olefination reactions lead via 1,2-addition to betaine structures **4** as zwitterionic intermediates that would form oxaphosphetane **3** with a final release of alkene and phosphine oxide by ring opening (*syn*-cycloreversion process), it has been seen more recently that especially under salt-free, aprotic conditions, many ylides undergo



© 2018 The Author(s). Licensee InTech. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. [cc] BY a  $\pi^2 s/\pi^2 a$  [2+2]-cycloaddition with the carbonyl component leading to the oxaphosphetane **3** directly [2], which in certain cases can be in equilibrium with betaine structures **4** (**Scheme 1**). In HWE reactions, the deprotonated phosphonate **6a** undergoes a nucleophilic addition to the carbonyl compound (e.g., **7**), which usually is the rate limiting step [3]. The elimination to the final products proceeds through oxaphosphetane **9** (**Scheme 2**). The Wittig olefination has been used industrially in the synthesis of terpenoids [4]. Recently, a one-pot synthesis of the vasodilator and anti-platelet agent Beraprost sodium, a prostacyclin analog, was communicated with the HWE reaction as the key transformation with the idea of using the approach in an industrial synthesis of the pharmaceutical [5].

For years after the discovery of the Wittig olefination [6, 7], most Wittig transformations were carried out under inert atmosphere using dry solvents such as THF [8], DME [9], diethyl ether [10] and benzene [11]. Later it was realized that stabilized and semi-stabilized Wittig reagents can be reacted in non-de-aerated solvents, where the solvents need not be dried specifically. Most of these conjugated Wittig reagents are thermally stable and tolerate water, air and mild oxidants, while maintaining reactivity towards aldehydes and often also towards ketones. This allows for a plethora of reaction conditions for many Wittig olefination reactions such as obviating solvents altogether [12, 13] or running the reactions in aqueous solutions [14, 15] or in mixed solvents [16]. Also, it permits one-pot transformations of Wittig olefinations in combination with other reactions, also because the stabilized and to some extent the semi-stabilized phosphoranes are inert to mild oxidizing and reducing agents. However, also with non-stabilized phosphoranes, where reactions have to be performed under the exclusion of air and moisture, Wittig reactions can be performed in conjunction with further transformations [17].

This chapter is to give an insight into the types of transformations that can be combined with Wittig- and Horner-Wadsworth-Emmons olefinations in Domino-, tandem and one-pot



Scheme 1. Schematic presentation of the reaction mechanism of the Wittig olefination.

Tandem-, Domino- and One-Pot Reactions Involving Wittig- and Horner-Wadsworth-Emmons...5http://dx.doi.org/10.5772/intechopen.70364



Scheme 2. General reaction mechanism of the HWE reaction.

reaction strategies. These include the preparation of phosphoranes and their reaction *in situ*, one-pot oxidation of alcohols to aldehydes and Wittig-olefination, *in situ*-recycling of phosphine oxides and catalytic Wittig reactions, one-pot Wittig-olefination metal catalyzed C–C bond forming reactions such as Suzuki-Miyaura, Sonogashira- and Heck reactions, Wittig and Horner-Emmons reactions in combination with polar cyclizations, Wittig-reactions carried out in combination with electrocyclic reactions, one-pot Wittig and Horner Emmons-addition reactions; cascade reactions featuring (triphenylphosphoranylidene)-ethenone and similar phosphoranes.

# 2. Wittig and Horner-Wadsworth-Emmons (HWE) olefination reactions with phosphoranes and phosphonates prepared *in situ*

Primarily, phosphoranes as Wittig reagents are prepared by the reaction of a triarylphosphine, usually triphenylphosphine, or, more seldom, a trialkylphosphine, and an alkyl halide with subsequent dehydrohalogenation of the triaryl(alkyl)alkylphosphonium halide produced. Non-stabilized Wittig reagents are not stable enough to be stored over longer periods of time; therefore, it is the norm that the Wittig-ylide is formed *in situ* from the oftentimes stable phosphonium salt, usually with a strong base, and then reacted directly with the carbonyl compound. In the case of stabilized phosphoranes, they are often stable enough to store, and the dehydrohalogenation necessitates only a weak base such as sodium carbonate or even sodium bicarbonate [18]. Nevertheless, this likewise allows the preparation of the phosphorane and the subsequent Wittig olefination in one pot [19], where even protic solvents can be used, such

as water. Similarly, semi-stabilized phosphoranes can be obtained *in situ* from their respective phosphonium salts, also even in aqueous medium, where LiCl promotes the Wittig olefination and suppresses the decomposition of the phosphoranes [14, 15]. Furthermore, all the catalytic Wittig reactions (see below) rely on the fact that the phosphorane is produced *in situ*.

Perhaps more interesting is the one-pot reaction of an alkyl halide, a phosphine and a carbonyl compound (Scheme 3). This can be achieved by consecutive addition of the components, when one or more of the components are sensitive, or by mixing of all components simultaneously. A consecutive addition of components in one pot was pursued by McNulty and Das who reacted air-sensitive triethylphosphine with benzyl bromides to the respective benzyltriethylphosphonium bromides, which were transformed to the phosphoranes with aq. NaOH, before being reacted with benzaldehydes to give (E)-stilbenes in an aqueous Wittig olefination [20]. Here, the triethylphosphine oxide by-product is water soluble. This reaction procedure has been diversified further by a one-pot preparation of benzyltriethylphosphonium bromides from the air-stable triethylphosphine hydrobromide and benzyl alcohols and subsequent Wittig olefination with aromatic aldehydes in aqueous medium [21]. Simultaneous mixing of alkyl halide such as  $\alpha$ -haloesters (e.g., 13),  $\alpha$ -halonitriles,  $\alpha$ -halocarbonyl compounds and  $\alpha$ -alkyl- $\alpha$ -halocarbonyl compounds, triphenylphosphine (12), and carbonyl compound (e.g., 11, 15, 18) in the presence either of a base [17, 22–26] or an alkene [27] was shown to give  $\alpha$ , $\beta$ -unsaturated esters [17, 22–27] (e.g., 14, 17, 19),  $\alpha$ , $\beta$ -unsaturated nitriles [23, 26] and enones [27], respectively (Scheme 3). Epoxides are stable under these reaction conditions as can be seen in the transformation of **18** to **19** (Scheme 1). A one-pot, fluoride catalyzed Wittigolefination has also been devised, where ethyl bromoacetate is reacted with carbaldehydes in the presence of tri-*n*-butylphosphine and tetrabutylammonium fluoride (Bu<sub>4</sub>NF) to give (*E*)configured  $\alpha,\beta$ -unsaturated esters in good yield [28]. The synthesis of  $\alpha,\beta$ -unsaturated esters has also been achieved from their alkyl halide and aldehyde constituents using tributylarsine [29] or a substituted triarylarsine instead of triphenylphosphine [30]. The use of tributylarsine in the presence triphenyl phosphite [29] led to the creation of a catalytic system which was



Scheme 3. In situ preparation of phosphoranes and subsequent Wittig olefination.

developed further with one-pot transformations that were managed with catalytic amounts (2 mol%) of poly(ethylene glycol) and (PEG)-supported tellurides in the presence of  $K_2CO_3$  as base [31–34]. Also, micellar reaction systems such as micellar solutions of sodium dodecyl sulfate (SDS) in water have been used, in which Wittig olefinations were carried out between aldehydes and phosphoranes, synthesized *in situ* [35, 36]. A. Galante has per Wittig reactions in the fluorous phase with *in situ* pre-formed perfluorinated ylides [37].

Traditionally, stabilized halophosphoranes have been prepared by the halogenation of the nonhalogenated parent phosphoranes and a subsequent dehydrohalogenation of the halogenated phosphonium salt obtained. Karama et al. have combined this *in situ* halogenation: dehydrohalogenation step with the Wittig reaction itself. Additionally, an *in situ* alcohol oxidation to provide the aldehyde starting material was integrated into many of these reaction sequences (**Scheme 4**) [38–42].



Scheme 4. One-pot oxidation, halogenation, and Wittig reaction to 2-haloacrylates.

# 3. *In situ* alcohol oxidation — Wittig/HWE reactions; other *in situ* aldehyde preparations run with subsequent Wittig/HWE sequences in one pot

The tolerance of stabilized phosphoranes towards mild oxidants allows for the oxidation of an alcohol to an aldehyde and its Wittig reaction in one-pot (**Schemes 5** and **6**). As oxidants, activated  $MnO_2$  [43–46], barium permanganate [47, 48], tetra-*n*-propylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO) [49–54] and TPAP/*N*,*N*,*N'*,*N'*-tetramethylenediamine dioxide (TMEDAO<sub>2</sub>) [55], *o*-iodoxybenzoic acid (IBX) [56–58], Dess-Martin periodinane [59–61], DMSO-oxalyl chloride (Swern conditions) [62–64], DMSO-SO<sub>3</sub>-pyridine (Parikh-Doering oxidation) [38, 39] or DMSO-SO<sub>3</sub>-triethylamine [65], pyridinium chlorochromate (PCC) or PCC/celite [66–69] as well as pyridinium dichromate (PDC) [70] such as PDC encapsulated in sol gel [71] have been used. In addition, metal catalyzed aerobic oxidation reactions of aldehydes with concomitant olefination reactions are known, where [(eta*p*-cymene)RuCl<sub>2</sub>]<sub>2</sub> (**27**) [72], nanoparticulate ruthenium supported on highly porous aluminum oxyhydroxide [73] or on silica gel [74], and nickel nanoparticles [75, 76] (**Scheme 6**) have been used as catalyst in the case of a concomitant Horner-Wadsworth-Emmons (HWE) reaction [77], Cu(I)-phenanthroline as a catalyst in an oxidation: HWE: sequential procedure [78].

Taylor et al. give a good overview of the tandem oxidation-Wittig processes developed until 2005, focusing especially on the tandem oxidation process (TOP) developed by his group [43–46],





Scheme 6. One-pot metal catalyzed oxidation of alcohols utilizing oxygen-Wittig reaction.

using activated  $MnO_2$  [79]. Over the years, this process has been used more often [40, 80–97] than the other processes shown above. Recently, also  $MnO_2$  derived molecular sieve material such as OMS-2 [KMn<sup>4+</sup>Mn<sup>3+</sup>O<sub>16</sub>·nH<sub>2</sub>O] has been used with success in aerobic, catalytic one-pot oxidation Wittig reactions of benzylic and allylic alcohols to the respective cinnamates [98]. Overall, the Wittig transformations of the aldehydes produced *in situ* allows for the manipulation of aldehydes that are inherently instable such as of silyl substituted aldehydes, propargyl aldehyde [97], and chiral  $\gamma$ -aminoaldehydes, the latter without loss of stereochemical integrity (**Scheme 5**) [89]. In the case of Wittig transformations of chiral  $\alpha$ -aminoaldehydes,  $\beta$ -aminoalcohols were oxidized to  $\alpha$ -aminoaldehydes with NaOCl in the presence of AcNH-TEMPO, where the crude  $\alpha$ -aminoaldehydes gained from the oxidation were subjected directly to olefination to give Wittig products without loss of stereochemical integrity [99–101].

Other preparation methods of aldehydes in conjunction with Wittig olefinations or HWE reactions have been reported. Thus, an oxidative cleavage of a glycol can be carried out in combination with a subsequent Wittig-olefination [102–105] (**Scheme 7**). Also a one-pot carboxylic acid to aldehyde reduction and Wittig reaction is known [106]. Finally, a Domino hydroformylation/Wittig olefination procedure has been developed, starting from allylamines (**Scheme 8**). The aldehyde is not isolated [107]. Domino/hydroformylation/Wittig olefination protocols have been introduced with other olefinic starting materials, also [108–110].



Scheme 7. Oxidative glycol cleavage—Wittig reaction.



Scheme 8. Hydroformylation—Wittig reaction.

## 4. Wittig- and HWE reactions and C—C-coupling reactions in one-pot procedures

Wittig- and Horner-Wadsworth-Emmons reactions can be combined with C—C-coupling reactions such as Suzuki cross-coupling [111–113], Mizoroki-Heck reaction [113–118] and Sonogashira-reaction [119]. Initially, it was observed that conjugated phosphoranes were stable under reaction conditions used for Heck- or Suzuki reactions (Scheme 9). Thus, phosphoranes themselves could be functionalized by Suzuki- [120], Mizoroki-Heck- [121], or Sonogashira-type [119] cross-coupling reactions, either in solution or when polymer-bound [122]. These phosphoranes could then be subjected to normal Wittig-olefination reactions with ketones or aldehydes [120–122]. The one-pot Wittig-Heck-reaction strategy can be extended to include an *O*-alkylation, where the Wittig reaction of a *p*-hydroxybenzaldehyde (43) with methylenetriphenylphosphorane, obtained *in situ* from phosphonium salt 44 provides the *p*-hydroxystyrene as the olefin component in the Mizoroki-Heck reaction in the presence of an alkyl bromide (e.g., 45), which *O*-alkylates the phenoxy-function to give alkoxystilbenes 46 (Scheme 9) [123].



#### 5. One-pot Wittig- and HWE olefination/cycloaddition reaction

One can easily visualize that an alkene prepared by a Wittig olefination can easily be used as a 2-pi component in cycloaddition reactions, in one pot (**Scheme 10**). A typical such cycloaddition is [4+2]-cycloaddition, such as the classical Diels Alder reaction, which can be performed both inter-[69, 124] and intramolecularly [125–132] in tandem with a Wittig-reaction.

Hilt and Hengst have published a cobalt(I)-catalyzed Diels Alder reaction of alkynyltriphenylphosphonium and 1,3-dienes with a consecutive Wittig reaction of the cycloadduct with Tandem-, Domino- and One-Pot Reactions Involving Wittig- and Horner-Wadsworth-Emmons...11http://dx.doi.org/10.5772/intechopen.70364



various aldehydes in one pot that lead after a further dehydrogenative step to substituted stilbenes and styrenes (**Scheme 11**) [133].

Interesting is the cycloaddition of *in situ* produced benzyne (**55**) to 1,4-diphenylbutadiene, prepared *in situ* by HWE reaction from cinnamaldehyde, (**15**) give 1,4-diphenylnaphthalene (**56**) (**Scheme 12**) [134].

The transformation sequence Diels-Alder/Wittig can be part of a more complex reaction chain. Thus, Ramachary and Barbas III [135] have forwarded a Domino Wittig/Knoevenagel/



Scheme 12. One-pot HWE reaction—cycloaddition of *in situ* produced benzyne.

Diels-Alder sequence to spirotriones **58** (**Scheme 13**) and a Wittig/Knoevenagel/Diels-Alder/ Huisgen cycloaddition sequence to polysubstituted triazoles **61** (**Scheme 14**).

Oxidation of benzyl alcohols to benzaldehydes can be incorporated into a Wittig-Diels Alder sequence [69]. Also, hetero-Diels-Alder reactions can be run in tandem with a Wittig olefination as shown by Ramachary et al. in their synthesis of tetrahydropyrans **64** (**Scheme 15**) [136]. Here, diamine **63** is used as a catalyst. The reaction, however, gives the product only in low enantiomeric excess (**Scheme 15**).

Huisgen type [3+2]-cycloaddition reactions can be run also in a simple tandem process rather than incorporated in a more complex reaction chain (see above). A typical example is shown in **Scheme 16**, where azidoethyl-tetrahydro-hydroxyfuran **66** is treated with phosphorane **21** to give triazoline **68** alongside diazoamine **69** [137]. Further such approaches are known [138, 139].



Scheme 13. Domino Wittig/Knoevenagel/Diels-Alder sequence.



Scheme 14. Wittig/Knoevenagel/Diels-Alder/Huisgen cycloaddition sequence.

Tandem-, Domino- and One-Pot Reactions Involving Wittig- and Horner-Wadsworth-Emmons...13http://dx.doi.org/10.5772/intechopen.70364



Scheme 16. Wittig reaction-intramolecular Huisgen type [3+2]-cycloaddition.

#### 6. One-pot Wittig- and HWE olefination/addition reaction

Electrophiles can be added to the alkene function obtained, in a one-pot reaction with the Wittig olefination. A typical example is the stereoselective bromination of the Wittig product with oxalyl bromide (71), where triphenylphosphine oxide (70) as side product of the olefination step acts as a catalyst in the bromination (**Scheme 17**) [140]. Hamza and Blum have developed a sol–gel entrapped tertiary phosphine by co-polycondensation of tetramethoxysilane, 2-diphenyl(phosphino)ethyltri(ethoxy)silane and *N*-2-(aminoethyl)-3-aminopropyltri(methoxy) silane. This could be reacted in a Wittig type olefination with benzyl chlorides (e.g., **76**) and benzaldehydes, prepared *in situ* from benzyl alcohols (e.g., **75**). The strategy allows for the combination of the process with a bromination step in one pot by addition of sol–gel-bound pyridinium hydrobromide perbromide after completion of the Wittig reaction (**Scheme 18**) [71].

Alternatively, the process can be combined with a hydrogenation step by the addition of hydrogen in the presence of an added heterogenized Wilkinson catalyst (**Scheme 19**) [141]. A further Wittig olefination—hydrogenation sequence was developed by Zhou et al. who obtained  $\alpha$ -CF<sub>3</sub>- $\gamma$ -ketoesters **82** by adding trichlorosilane to the reaction mixture where triphenylphosphine oxide (again as side product of the Wittig olefination) acts as a Lewis base and activates the silane as hydrogenating agent (**Scheme 20**) [142]. The routine was expanded to other aldehydes including alkanals as educts [143]. This reaction was also carried out with



**Scheme 17.** Wittig olefination – Ph<sub>3</sub>PO-catalyzed addition of bromine.



Scheme 19. Wittig olefination—hydrogenation.

glyoxal derivatives **84** as starting materials, where after conjugate addition of trichlorosilane a few drops of methanol were added to the solution resulting in conversion of the trichlorosilylenol ether (**86**) to the keto compound **87** while at the same time generating HCl, which then promoted a Paal-Knorr reaction of **87** to the furan **88** (**Scheme 21**) [144].

Tandem-, Domino- and One-Pot Reactions Involving Wittig- and Horner-Wadsworth-Emmons...15http://dx.doi.org/10.5772/intechopen.70364



Scheme 20. Wittig reaction-triphenylphosphine oxide catalyzed hydrogenation.



Scheme 21. Furan synthesis by one-pot Wittig olefination-hydrogenation-Paal-Knorr reaction.

Lu and Toy showed that the Wittig-olefination—trichloromethylsilane conjugate addition sequence can be coupled with the initial preparation of the phosphorane in one pot [145]. The conjugate addition to furnish the silyl enol ether can be combined with a reductive Aldol reaction, where for the Wittig reaction and for the reductive Aldol reaction two separate aldehydes can be used (**Scheme 22**) [145]. The reactions above can be run with a triarylphosphine-tertiary amine bifunctional polymeric reagent (Rasta-Resin-PPh<sub>3</sub>-NBn<sup>i</sup>Pr<sub>2</sub>), where the polymer bound triarylphosphine oxide also exerts a catalyzing effect on the addition of Cl<sub>3</sub>SiH while making it possible to recycle the polymer [146].

As many Wittig olefinations can be performed in aqueous medium, it is possible to combine the reaction with an enzymatic step. One such sequence is the enzymatic reduction of the olefinic moiety by a recombinant enoate reductase from *Gluconobacter oxydans*, carried out with an enzyme-coupled *in situ* cofactor regeneration with a glucose dehydrogenase as enzyme component and p-glucose as co-substrate (**Scheme 23**) [147].

Interestingly, a Wittig reaction can also be run in combination with an enzymatic reduction, where the *in situ* prepared enone **93** is transformed to the alkenol **94** (**Scheme 24**) [148].



Scheme 23. Wittig-olefination-enzymatic ene-hydrogenation.



The possibility of a combination of a Wittig/HWE olefination and a Michael addition has been studied by a number of research groups. Thus, Piva and Comesse have added phosphonoesters to copper enolates derived from the 1,4 addition of cuprates **97** to enones **96** with the idea that the enolate would deprotonate the phosphonoester **98** producing the reactive ketone and phosphonate, which undergo HWE reaction. Products **99** of the tandem Michael-HWE reaction are produced in acceptable yield (**Scheme 25**) [149, 150]. This strategy was used with *p*-methylcinnamaldehyde (**100**) as carbonyl component in the total synthesis of (±)-*ar*-turmerone (**105**), a bisabolane-type natural product found in *Zingiber* and *Curcuma* species (**Scheme 26**) [151].

Tandem-, Domino- and One-Pot Reactions Involving Wittig- and Horner-Wadsworth-Emmons...17http://dx.doi.org/10.5772/intechopen.70364



Scheme 25. One-pot Michael addition-HWE reaction.



Scheme 26. Synthetic route to utilizing a one-pot Michael addition—HWE reaction.

#### 7. One-pot Wittig-olefination/functional group interconversion

Wittig reactions can be performed with alkoxycarbonylmethylidenetriphenylphosphorane (**21**) in aq. NaOH, where the cinnamates formed are hydrolysed *in situ* to cinnamic acids **106** (**Scheme 27**) [152]. After completion of the reaction, triphenylphosphine oxide can be filtered off from the strongly basic, aqueous solution, and the cinnamic acids are isolated by simple filtration after acidification of the filtrate. Pinacol-acetal tripropylphosphonium salt **107** has been reacted in aq, 1 M NaOH with different benzaldehydes **37**; the cinnamaldehyde *O*,*O*-pinacol acetal can be hydrolyzed directly to the cinnamaldehydes **108** with 25w% aq. H<sub>3</sub>PO<sub>4</sub> (**Scheme 28**) [153].

This procedure provides a nice alternative to the reaction of benzaldehydes with triphenylphosphoranylideneacetaldehyde, which often produces dienals and trienals as side-products. A tandem Wittig-cyanosilylation was developed by Zhou et al., where again Ph<sub>3</sub>PO as side product of the Wittig olefination acts as Lewis base to catalyze TMSCN in the cyanosilylation step. Chiral salen



Scheme 28. One-pot Wittig reaction – acetal hydrolysis.

aluminum catalyst **109** was used as Lewis acid to activate the keto function in the cyanosilylation. Products were obtained with high enantioselectivity [68–93%ee]. TMSCN and chiral catalyst **109** were added after completion of the Wittig reaction, albeit in one pot (**Scheme 29**) [143].

As Wittig reactions can be carried out in aqueous medium, enzymatic reactions can be integrated into the process (*vide supra*). In this regard, M. Kraußer et al. showed that 4-phenylbut-3-en-2-ones (**93**), obtained by Wittig olefination, are reduced to the corresponding 4-phenylbut-3-en-2-ols (**94**) in >99 ee(%) using (*S*)-alcohol dehydrogenase [(*S*)-ADH] from *Rhodococcus* sp. or (*R*)-ADH from *Lactobacillus kefir* [148].



Scheme 29. Wittig reaction-cyanosilylation.

#### 8. One-pot Wittig- and HWE olefination/cyclization

*Michael type cyclization*—cyclic hemiacetals can be used efficiently as substrates in Wittig olefination reactions with stabilized Wittig reagents. After the Wittig reaction, the tethered alcohol function induces a cyclization through a Michael reaction. This reaction sequence has been used especially in the construction of functionalized C-glycosides such as in the stereospecific synthesis of  $\omega$ -amino- $\beta$ -p-furanoribosylacetic acid derivative **115** (**Scheme 30**) [154].

In their synthesis to C-glycoside amphiphiles, Ranoux et al. followed a similar strategy, reacting non-protected sugars with HWE reagents in aqueous or solventless conditions, leading to C-glucosides **117** and **121** (**Scheme 31**) [155].

A different mechanism to C-glucosides operates when 5,6-dideoxy-5,6-anhydro-6-nitro-D-glucofuranose **122** is reacted with an excess of phosphorane **21**. Here, **21** acts as a base and **122** experiences an anion driven ring opening to **123**, which undergoes an oxy-Michael addition to **124** with concomitant Wittig reaction, resulting in C-vinyl glycoside **125** (**Scheme 32**) [156].

A highly stereoselective tandem Wittig-reaction-Michael addition has been developed by Liu et al. [157] when reacting 3-carboxy2-oxopropylidene)triphenylphosphorane **126** with







Scheme 31. Synthesis of C-glucosides with a HWE-ring closure reaction.



Scheme 32. Tandem oxy-Michael addition-Wittig reaction.

enaldehydes (e.g., **15**), using a chiral pyrrolidine-based catalyst such as **128** (**Scheme 33**). Most likely, the asymmetric Michael addition proceeds by the reaction of **15** with the iminium compound **129** (**Scheme 33**), formed from **15** with catalyst **128**.

Beltrán-Rodil et al. have elaborated a retro-aldol initiated Wittig-olefination-Michael addition sequence leading to an exchange of the hydroxyl function in **130** for a carbalkoxymethyl group in **134**. The retro-aldol reaction is effected by the commercially available trimethylamine *N*-oxide (TMAO, **131**) [158] (**Scheme 34**).

*Electrocyclizations, incl. photocyclizations, and pericyclic reactions*: Electrocyclization can be run in concert with Wittig reactions. One such example is shown in **Scheme 35**, where allylic bromide **135**, the product of a Morita-Baylis-Hillman transformation, is converted with triphenylphosphine to the corresponding phosphonium salt, which is reacted with benzaldehyde (**11**) to give triene **136**. **136**, heated under aeration, undergoes a  $6\pi$ -electrocyclization—base catalyzed aerobic oxidation to *o*-terphenyl derivative **137** (**Scheme 35**) [159].



Scheme 33. Asymmetric Michael-addition-Wittig-olefination.

Tandem-, Domino- and One-Pot Reactions Involving Wittig- and Horner-Wadsworth-Emmons...21http://dx.doi.org/10.5772/intechopen.70364



**Scheme 35.** One-pot phosphorane synthesis – Wittig-reaction –  $6\pi$ -electrocyclization – oxidative dehydrogenation.

Similarly, Hamza and Blum [71], who developed a Wittig olefination with a sol-gel entrapped tertiary phosphine derived phosphorane (*vide supra*, **Schemes 18** and **19**) showed that the Wittig reaction can be run in concert with a photochemical cyclization under aerobic conditions to produce phenanthrene (**138**) (**Scheme 36**) [71].

A number of tandem Wittig/HWE reaction—Claisen/Cope rearrangements have been reported [160–173]. A typical example is shown in **Scheme 37**, where neat (4-fluorophenoxy-acetyl)cyanomethylene)triphenylphosphorane **139** is subjected to microwave irradiation at 450 W in a sealed tube to undergo an intramolecular Wittig reaction—Claisen rearrangement to furnish benzofuran **134** (**Scheme 37**) [173].

Mali et al. achieved the synthesis of seselin and angelicin derivatives (e.g., **148** and **150**) by a tandem Wittig-olefination—Claisen rearrangement from propargyl and chloroalkyl ethers of 2,4-dihydroxybenzaldehyde and 2,4-dihydroxyacetophenone (e.g., **146** and **149**) (Scheme 38) [164].

Nevertheless, sometimes, these reactions are not easy to control. Thus, a cascade of Wittig reaction and double Claisen and Cope rearrangements starting from 2,4-prenyloxybenzaldehyde



Scheme 36. Wittig olefination – photocyclization – oxidative dehydrogenation.



Scheme 37. Intramolecular Wittig reaction—Claisen rearrangement.



Scheme 38. One-pot syntheses of seselin and angelicin derivatives.

**151** leads to a plethora of products through the range of reactions that are possible with the intermediate **153**, itself produced through the Wittig reaction and a first Claisen rearrangement. The final products found include gravelliferone (**154**, 10%), balsamiferone (**155**, 5%), and 6,8-diprenylumbelliferone (**156**, 15%) (**Scheme 39**) [169].

Less common is the tandem Wittig and ene reaction. Tilve et al. have published such a combination of Wittig and ene reaction in their total synthesis of (±)-kainic acid (160), an amino

Tandem-, Domino- and One-Pot Reactions Involving Wittig- and Horner-Wadsworth-Emmons...23http://dx.doi.org/10.5772/intechopen.70364



Scheme 39. Wittig reaction-double Claisen and cope rearrangements.

acid found in different species of red algae [174]. Here, the product was formed in 65% yield as a mixture of diastereoisomers **1598a/159b** in a ratio of 1:5. Previously, the authors had synthesized (±)-kainic acid (**160**) utilizing a Wittig—Michael reaction as the key step (**Scheme 40**) [175].

Finally, the possibility of a tandem Wittig-olefination—aza-Wittig rearrangement should be mentioned—this combination was carried out on 2-benzoylaziridine **161** to give stereoiso-meric dehydropiperidines **163/164** (**Scheme 41**) [176].



Scheme 40. Wittig-ene cascade as a key step towards the synthesis of kainic acid (160).



A wealth of further transformations have been found to be possible in combination with Wittig/HWE reactions. Thus, cyclopropanation of alkenes using sulfur-ylide reagent **166** can be run in tandem with a Wittig reaction with a conjugated phosphorane such as **21**. This combination of reactions can be performed with the preparation of the aldehyde as the Wittig substrate by oxidation of the corresponding alcohol **165** with MnO<sub>2</sub> in one pot (**Scheme 42**) [177].



Scheme 42. One-pot oxidation-Wittig-olefination-cyclopropanation.

Generally, non-stabilized phosphoranes are basic. This basicity has been used by Knüppel et al. in the transformation of  $\alpha$ , $\alpha$ -dibromoenone **168** with excess methylenetriphenylphosphorane, where the phosphorane induces a Corey-Fuchs-reaction-type dehydrobromination/debromination to generate a terminal alkyne, which together with the concomitantly run Wittig-olefination delivers **169**, an intermediate to the trisnorsesquiterpene (–)-clavukerin A (**171**) (**Scheme 43**)



Scheme 43. Wittig-olefination – Corey-Fuchs-reaction-type dehydrobromination/debromination.

[178]. A metathesis reaction completes the sequence to **171**. In this case, the metathesis reaction is not run in one pot with the previous transformations.

Nevertheless, one-pot Wittig—metathesis reactions are well known from the literature [179–181]. A typical example is shown in **Scheme 44**, where catalyst **174** serves both as a catalyst for the metathesis as well as for the Wittig olefination, when the *in situ* produced aldehyde **175** is treated with triphenylphosphine and ethyl diazoacetate (**176**) in one pot (**Scheme 44**).



Scheme 44. One-pot Wittig-Metathesis reaction.

#### 10. Conclusion

Due to the fact that phosphoranes and phosphonates are stable under more diverse conditions than was initially realized, it has become possible to perform reaction cascades and one-pot reactions with Wittig- and HWE reactions as an integral part of the reaction sequence. Frequently, Wittig olefination reactions are carried out with *in situ* prepared phosphonium salts and phosphoranes [17, 22–27]. One-pot oxidation – Wittig olefination reactions are also quite common [40, 43-110], especially when the carbonyl component is labile [89, 97]. Often, the oxidant of choice is MnO<sub>2</sub> [40, 43–46, 79–97], although a number of reactions are known where transformations were carried with air oxygen using metals and metal oxides as catalysts [72–78]. As many Wittig- and HWE reactions tolerate metal catalysts, this allows the running of Wittig/HWE reactions in combination with metal catalyzed cross coupling reactions and olefinations such as Heck [114–123], Suzuki [111–113], Sonogashira [119–121], and metathesis reactions [179–181]. The alkenes gained in the olefination reactions can be submitted to cycloaddition reactions, including Diels Alder reactions [69]. Furthermore, the alkenes lend themselves to 1,2-addition reactions [71, 140] in one-pot procedures. In cases where enones or enaldehydes are produced in the olefination reaction, a 1,4-addition becomes a possibility; this includes the Michael addition [149–151]. Also, the combination of ring opening of cyclic hemiacetals or acetals, olefination reaction and a 1,4-addition leading to ring closure is quite common [154–156]. The outcome of one-pot sequences of olefination reaction-electrocyclic rearrangement can be predicted less easily. Nevertheless, one-pot Wittig olefination-Claisen- [173], Wittig olefination-Cope- [169], and Wittig olefination-aza Wittig [176] rearrangement reactions have been published. Lastly, Wittig olefination and HWE reactions have been combined with functional group transformations, including the hydrolysis of an ester function [152] and the reduction of a carbonyl group [148].

The prospects of multi-step, one-pot reactions and reaction cascades incorporating Wittig reagents can be seen in the rich chemistry of ketenylidenetriphenylphosphorane (**178**) (**Scheme 45**) [182–185], which has been reviewed earlier [182, 186, 187]. Lastly, catalytic Wittig reactions can be seen as a subset of tandem reactions involving phosphoranes. Further research in specifically this area will help make the Wittig olefination more atom-economical and environmentally sustainable, so that this reliable alkene forming reaction will remain a competitive olefination strategy of choice.



Scheme 45. Cascade reactions with ketenylidenetriphenylphosphorane (178).

#### Author details

Fatima Merza<sup>1</sup>, Ahmed Taha<sup>2</sup> and Thies Thiemann<sup>1\*</sup>

- \*Address all correspondence to: thies@uaeu.ac.ae
- 1 Department of Chemistry, College of Science, United Arab Emirates
- 2 UAEU Libraries, United Arab Emirates University, Al Ain, United Arab Emirates

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