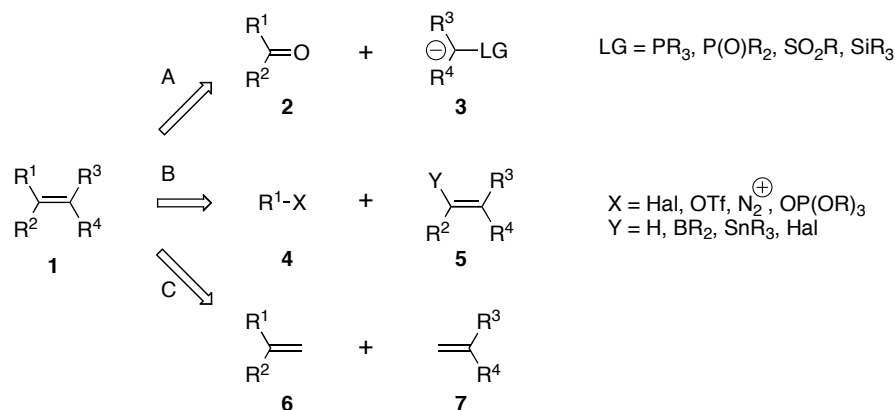
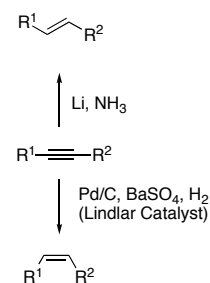


## Chapter 13: Olefinations

### 13.1. Introduction

Ever since Georg Wittig back in 1953 pioneered the first olefination of a carbonyl compound,<sup>1</sup> the synthesis of alkenes has become an indispensable strategic tool for the construction of complex molecules. While alkenes can be obtained by functional group transformations, most notably by selective hydrogen transfer to alkynes, the most powerful olefination reactions proceed by concurrent carbon-carbon formation.

There are three general strategies that allow the synthesis of alkenes with a broad structural variety and functional group tolerance, which each emerged approximately two decades apart from each other. The reaction of carbanions **3**, being stabilized by an electron withdrawing group LG that acts at the same time as a good leaving group, with aldehydes or ketones **2** has been for more than 50 years a most reliable tool for alkene synthesis (Scheme 1, strategy A).<sup>2</sup> Depending on the group LG, these transformations are known as Wittig reaction (LG = PR<sub>3</sub>),<sup>3</sup> for which the Nobel Prize was awarded in 1960, Horner-Wittig reaction (LG = P(O)Ph<sub>2</sub>), Horner-Wadsworth-Emmons (HWE) reaction (LG = P(O)(OR)<sub>2</sub>),<sup>4</sup> Julia Olefination (LG = SO<sub>2</sub>R),<sup>5</sup> or Peterson Olefination (LG = SiR<sub>3</sub>).<sup>6</sup> Related to this strategy are carbonyl olefination reactions with metal carbene, carbenoid or *gem*-dimetal complexes, making use e.g. of titanium (Tebbe reagent), zinc, chromium, or zirconium. Reductive coupling reactions of carbonyl compounds using low valent titanium, most notably the McMurry reaction, have also seen a spectacular development over the years, beginning with the synthesis of symmetrical, unfunctionalized alkenes up to complex applications in natural product synthesis with high functional group tolerance.<sup>7</sup>



**Scheme 1.** Widely used strategies for olefinations

In the seventies, transition metal catalyzed cross coupling reactions with alkenes **5** entered the synthetic arena (Scheme 1, strategy B).<sup>8</sup> Direct coupling of alkenes (Heck reaction: Y = H) or alkenyl metals (Stille reaction: Y = SnR<sub>3</sub>; Suzuki-Miyaura reaction: Y = BR<sub>2</sub>; Negishi reaction Y = ZnR) with appropriately activated aryl, alkenyl or even alkyl substrates **4** has been developed into most economic processes, which have found not only manifold examples as

key steps in natural product synthesis but are used in industrial large scale applications for common intermediates such as styrenes as well.

With the discovery of robust and readily available catalysts, about a decade ago molybdenum (Schrock) and especially ruthenium (Grubbs), catalyzed metathesis reactions (Scheme 1, strategy C) initiated a change in paradigm not only for the synthesis of alkenes, but also for the assembly of complex structures such as carbo- and heterocycles.

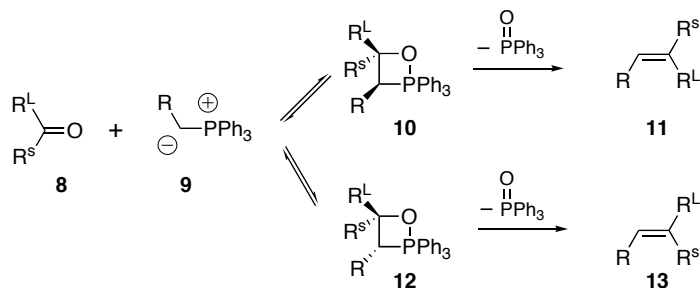
### 13.2. Olefination of carbonyl compounds with phosphorus reagents

#### 13.2.1. The Wittig reaction

The reaction of phosphonium ylides with carbonyl compounds – named after its inventor the Wittig reaction – is one of the most reliable methods for the synthesis of alkenes. It occurs with complete regioselectivity, i.e. the carbonyl group of the substrate is replaced by the alkene group without that double bond isomerizations occur, and also the double bond geometry can be controlled to a large extent.

There has been a heated debate on the mechanism of the Wittig reaction, which is still ongoing even today. The controversy is centered around the intermediate that is formed after addition of the ylide to the carbonyl compound, i.e. if the betaine plays a role along the reaction pathway, or if the phosphaoxetane is directly formed in a formal [2+2]cycloaddition. Based on low temperature  $^{31}\text{P}$  NMR studies and calculations, and also supported through X-ray structures of phosphaoxetanes the scales have been tipped over in favor of the latter not only as being the decisive intermediate prior to alkene formation through elimination of phosphinoylide.

Thus, the currently accepted mechanism for the Wittig reaction is the formation of the phosphaoxetanes **10** and **12**, which stereospecifically collapse to the *Z*- or *E*-alkenes **11** and **13** (Scheme 2). The sterically more crowded *cis*-phosphaoxetane **10** is apparently kinetically favored over the *trans*-phosphaoxetane **12** for reasons not yet fully understood. Consequently, non-stabilized ylides **9** will follow a kinetically controlled pathway *via* **10** to give preferentially rise to (*Z*)-alkenes **11**. With stabilized ylides an equilibration of the diastereomeric phosphaoxetanes **10** and **12** is reached *via* back reaction to **8** and **9**, thus ultimately favoring the formation of (*E*)-alkenes **13** *via* the sterically less crowded **12** under thermodynamic control (Table 1). As a notable exception,  $\alpha$ -alkoxyaldehydes give rise to *Z*-alkenes, especially when the reaction is carried out in protic solvents.



Scheme 2. The mechanism of the Wittig reaction

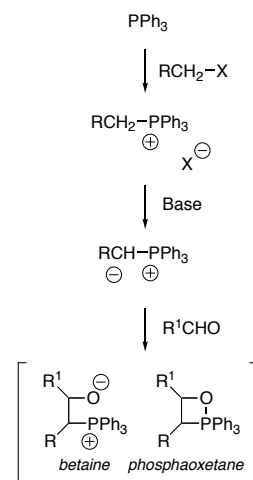


Chart 1. Definition of stabilized and non-stabilized ylides



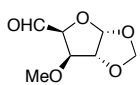
**non-stabilized ylides:**

*R* = H, Alkyl, Aryl  
salt free (*M*≠Li)  
generated *in situ*  
react with aldehydes and ketones

**stabilized ylides:**

*R* = electronwithdrawing group  
e.g. CO<sub>2</sub>R, COR, CN  
can be isolated and subsequently  
reacted with aldehydes

**Table 1.** Wittig reaction of aldehydes **8** with phosphonium ylides **9**

| <b>8:</b> R <sup>L</sup> /R <sup>S</sup>  | <b>9:</b> R        | MX/solvent        | <b>11:13</b> ( <i>E/Z</i> ) | Yield (%) | Ref. |
|---|--------------------|-------------------|-----------------------------|-----------|------|
| -(CH <sub>2</sub> ) <sub>8</sub> -OAc/H   | <i>n</i> -Pent     | NaHMDS/THF        | 2:98                        | 79        | 9a   |
|  | CO <sub>2</sub> Et | DMF               | 86:14                       |           | 9b   |
|   |                    | CHCl <sub>3</sub> | 60:40                       |           |      |
|   |                    | MeOH              | 8:92                        |           |      |

Nevertheless, the synthesis of (*E*)-alkenes from non-stabilized ylides can be achieved using the Schlosser modification,<sup>10</sup> which calls for the presence of lithium salts to form the betaine, followed by a deprotonation/reprotonation sequence under kinetically controlled conditions in order to drive the reaction the *trans*-phosphaoxetane *trans*-**15**.

**Chart 2.** Factors that control the alkene geometry in the Wittig reaction

***E*-alkenes**

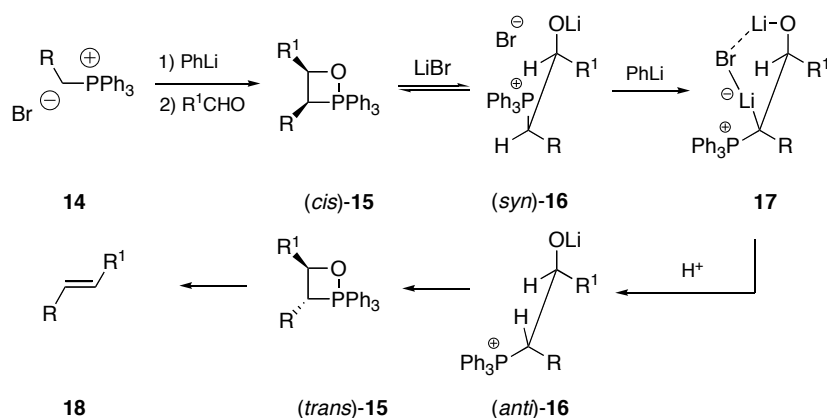
stabilized Ylides  
aprotic solvents  
catalytic amounts PhCO<sub>2</sub>H  
Schlosser modification

***Z*-alkenes**

non-stabilized ylides  
salt free conditions (M≠Li)  
sterically bulky aldehydes

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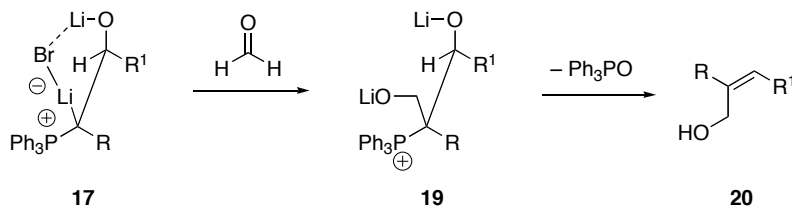


**Chart 3.** Examples for the Schlosser modification of the Wittig reaction (*cf.* Scheme 3)

| R              | R <sup>1</sup> | Y (%) | <i>E/Z</i> |
|----------------|----------------|-------|------------|
| Me             | <i>n</i> -Pent | 70    | 99:1       |
| <i>n</i> -Pent | Me             | 60    | 96:4       |
| <i>n</i> -Pr   | <i>n</i> -Pr   | 72    | 98:2       |
| Me             | Ph             | 69    | 99:1       |
| Et             | Ph             | 72    | 97:3       |

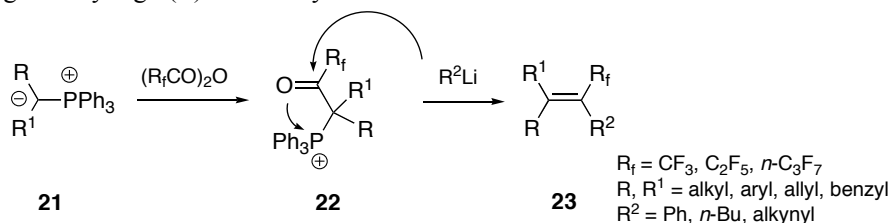
**Scheme 3.** The Schlosser modification of the Wittig reaction

A very useful extension of this variant is to trap **17** with formaldehyde, resulting in the formation of *Z*-configured allylic alcohols (Scheme 4).<sup>11</sup> It is important to note that only the secondary alkoxide in **19** forms an oxaphosphetane that subsequently eliminates triphenylphosphine oxide to yield the alkene **20**.

**Scheme 4.** Synthesis of *Z*-allylic alkenes from aldehydes

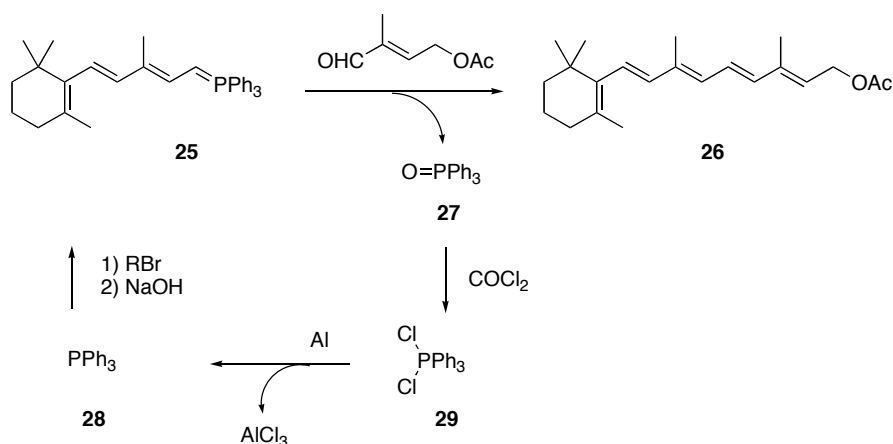
The synthesis of alkenes with perfluoroalkyl groups is usually not possible by direct Wittig reaction, since such substituents in  $\alpha$ -position are

stabilizing the ylide too strongly to render it nucleophilic enough to react with carbonyl compounds. Perfluoralkylated  $\beta$ -ketophosphonium ylides, however, provide a solution for the synthesis of such alkenes, demonstrating in an interesting way alternative applications of commonly employed phosphor ylides (Scheme 4).<sup>12</sup> Thus, ylides **21** can be acylated with perfluoroalkyl substituted acid anhydrides to yield  $\beta$ -ketophosphonium salts **22**, which have a sufficiently high carbonyl reactivity to be attacked by nucleophiles to form alkenes **23** with generally high (*E*)-selectivity.<sup>13</sup>



**Scheme 5.** Synthesis of perfluoroalkyl substituted alkenes

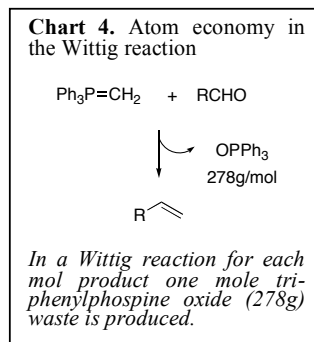
Despite the great synthetic versatility there is one significant disadvantage that has hampered the application of the Wittig reaction on industrial scale: As a byproduct triphenylphosphine oxide is formed, disfavoring this transformation under the aspect of atom economy. A convincing solution for large-scale applications of the Wittig reaction was developed by BASF AG in the synthesis of **26** as a precursor towards Vitamin A. Triphenylphosphine oxide (**27**) is recycled by chlorination with phosgene, followed by reduction of the resulting dichloride (**29**) with aluminum metal to give back triphenylphosphine (**28**) along with aluminumtrichloride that is further used as a catalyst for Friedel-Crafts acylations of aromatic compounds.



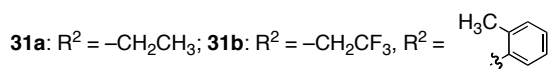
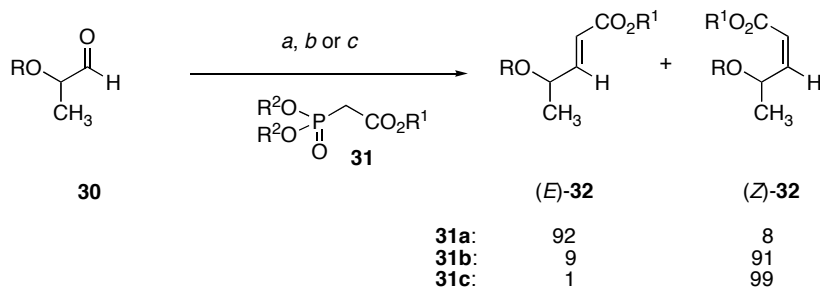
**Scheme 6.** Synthesis of the Vitamin A precursor **26**

### 13.2.2. The Horner-Wadsworth-Emmons reaction

An analogous olefination of carbonyl compounds can be achieved if phosphonates instead of phosphonium ylides are used (Horner-Wadsworth Emmons – *HWE* – reaction) are used, however, distinct differences to the Wittig

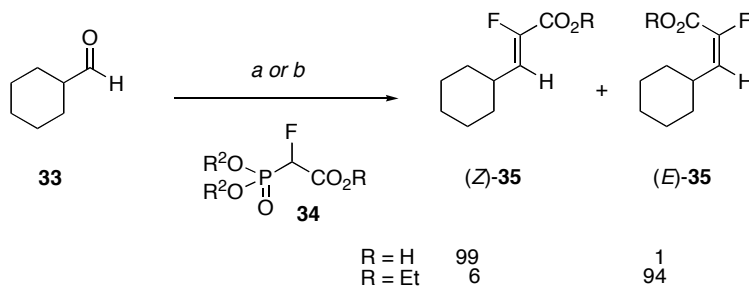


reaction previously described exist. Carbanions obtained upon deprotonation of a phosphonate are generally much more reactive than phosphonium ylides, so that they need to be stabilized by an electron withdrawing substituents in order to give useful yields in a subsequent reaction with either an aldehyde or a ketone. As byproduct water soluble phosphates are formed which greatly facilitates the workup of the products. The stereoselectivity of the HEW-reaction can be controlled by the steric and electronic properties of the alcohol groups  $R^2$  in the phosphonate: While alkyl groups, especially bulky ones like *i*-Pr, generally result in high *E*-alkenes, trifluoroethyl or aryl groups or the use of cyclic phosphonates will lead preferentially to *Z*-alkenes.



**Scheme 7. Reagents and Conditions:** (a) **31a**, NaH, THF, 83%; (b) **31b**, KH, THF, 84%; (c) **31c**, NaH, NaI, 88%.

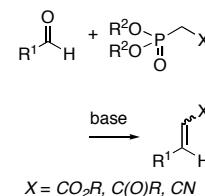
A remarkable control of stereoselectivity with  $\alpha$ -fluorinated phosphonates **34** has been reported solely by a combination of the appropriate choice of the group R and the base used for its deprotonation.



**Scheme 8. Reagents and Conditions:** (a) **34** ( $R = H$ ),  $Pr^iMgBr$ , 84%; (b) **34** ( $R = Et$ ),  $Bu^tLi$ , 83%.

Masamune and Roush first developed a very useful variant that allows carrying out the HWE-reaction with phosphonates **31** under mild basic conditions. Chelation of the carbonyl and the phosphonate oxygen with LiCl of  $MgBr_2$  activates **31** sufficiently to allow its deprotonation with weak bases such as triethylamine, and subsequent reactions with aldehydes yields predominantly *E*-alkenes.<sup>14</sup> The activation by Lewis acids is not even necessary if the reaction is carried out at high pressure.<sup>15</sup>

#### Chart 5. The HWE-reaction



#### *E*-alkenes

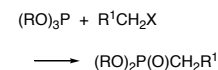
Bulky alkyl groups  $R^2$   
Bulky groups X

#### *Z*-alkenes

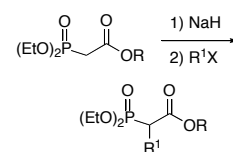
$R^2 = -CH_2CF_3$  (*Still-Genari*)  
 $R^2 = -Ar$ ; (*Ando*)  
Cyclic phosphonates

#### Chart 6. Common methods for the synthesis of phosphonates

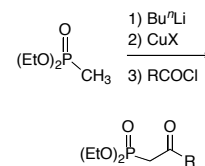
##### a) Michaelis-Arbuzov Reaction



##### b) Alkylation of phosphonates

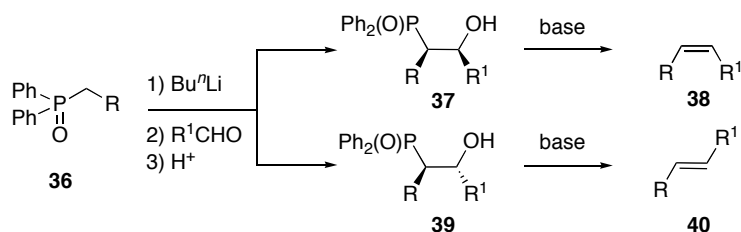


##### c) Acylation of phosphonates



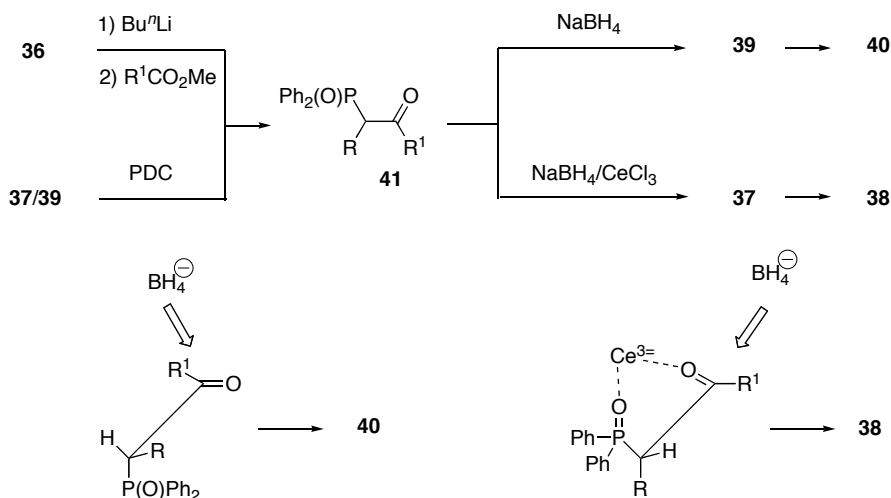
### 13.2.3. The Horner-Wittig reaction

Phosphine oxides are yet another class of phosphorus reagents that can be used for carbonyl olefinations, a process that is known as Horner-Wittig reaction. Mechanistically similar to the Wittig and the HWE reaction, an important difference is the possibility to isolate the intermediate  $\beta$ -hydroxy phosphine oxides, when lithium bases and low temperatures are employed. Subsequently, **37** and **39** can be individually transformed after separation by chromatography to the *Z*-alkene **38** or the *E*-alkene **40**, respectively.



**Scheme 9.** Lithium bases in the Wittig-Horner reaction.

Like the Schlosser variation in the Wittig reaction, there is also the possibility to obtain preferentially *E*-alkenes **40** from non-stabilized phosphine oxides. Oxidation of the mixture of **37/39** to  $\beta$ -ketophosphine oxides **41**, being also accessible directly from **36** by a Claisen type ester condensation, followed by reduction with  $\text{NaBH}_4$  preferentially gives rise to **39**, which can be explained by applying the Felkin-Anh-model.<sup>16</sup> Complementary to this, if the reduction is carried out using  $\text{CeCl}_3/\text{NaBH}_4$  (Luche reduction) **37** is preferentially obtained via chelate control, which collapses to the *Z*-alkene **38**.



**Scheme 10.** Warren variation of the Horner-Wittig reaction.

There are numerous examples for the application of Wittig-type olefinations in natural product synthesis.<sup>17</sup> A particular impressive example can

**Chart 7.** Factors that control the alkene geometry in the Wittig-Horner reaction

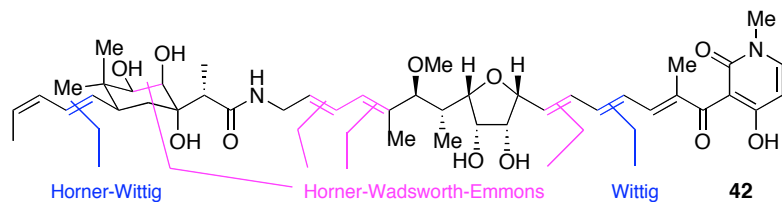
***E*-alkenes**

R anion stabilizing, moderate temperatures, non-Li base, thermodynamic control  $\rightarrow$  one-step protocol

***Z*-alkenes**

R not anion stabilizing, low temperatures, Li base, kinetic control  $\rightarrow$  two-step protocol

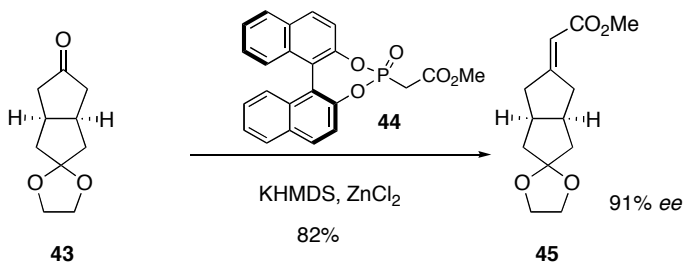
be found in the synthesis of the antibiotic aurodox (**42**) from the Nicolaou group, in which in a total of six olefination reactions all three Wittig variants were applied.



### 13.2.4 Asymmetric Wittig-type reactions

On a first glance, one might think that asymmetric olefination reactions are a contradiction in terms since no chiral centers are created by alkenylating a carbonyl group. However, by symmetry-breaking strategies, either by differentiating *meso*-compounds or, in a kinetic resolution, racemic carbonyl compounds asymmetric processes can be developed.<sup>18</sup> Most successfully, asymmetric Horner-Wadsworth-Emmons reactions have been developed, making use of three principle strategies to render a phosphonate chiral: (a) Introducing a C<sub>2</sub>-symmetrical, chiral auxiliary in place of the alkoxy groups in the phosphonate; (b) introducing a non C<sub>2</sub>-symmetrical, chiral auxiliary in place of the alkoxy groups in the phosphonate, thus making the phosphorus atom itself a chiral center; (c) introducing a chiral auxiliary in the part of the phosphonate that is subsequently transferred to the carbonyl compound.

Phosphonates, being rendered chiral by BINOL<sup>19</sup> or the corresponding phosphonic acid bis(amides)<sup>20</sup> bearing C<sub>2</sub>-chiral 1,2-diamines instead of diols are particularly effective for the desymmetrization of prochiral carbonyl compounds. Thus, upon deprotonation with KHMDS and subsequent reaction with **43**, the alkene **45** is obtained. Zinc chloride was found to be an effective additive, ensuring in general high yields and selectivities in such transformations.

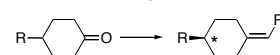


**Scheme 11.** Asymmetric HWE-reaction with phosphonates bearing a C<sub>2</sub>-symmetrical chiral auxiliary

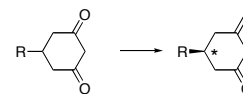
The camphorquinone modified phosphoramidate **47** also promotes olefinations with high selectivity (Scheme 11).<sup>21</sup> The better enantioselectivity obtained in the transformation of cyclohexanone **46** to **48** in comparison to the use of **44** might very well reflect the greater proximity of the chiral information to the reaction centers, being manifested in a stereogenic phosphorus atom in **47**.

**Chart 8.** Strategies for asymmetric olefination reactions

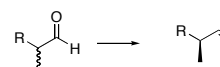
1. Prochiral carbonyl group differentiation

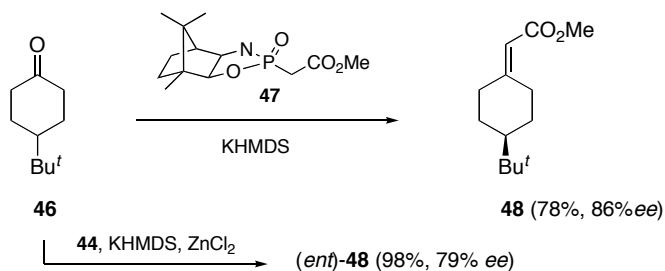


2. Enantiotopic carbonyl group differentiation



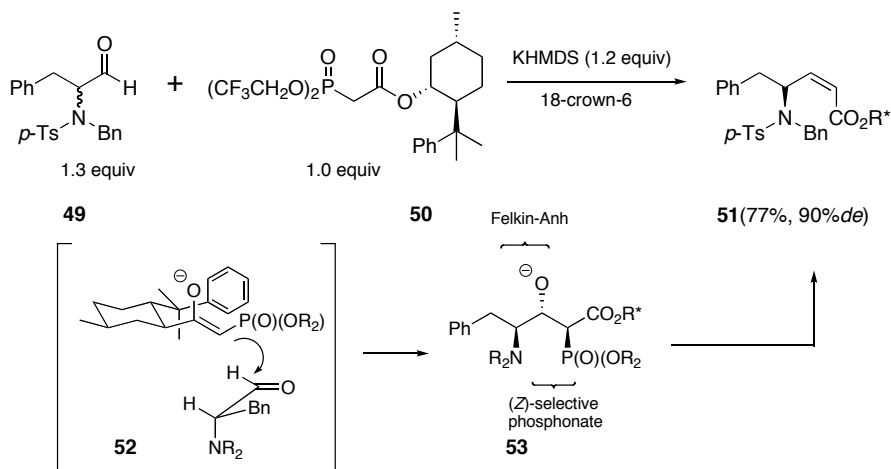
3. Kinetic resolution





**Scheme 12.** Asymmetric HWE-reaction with phosphonates bearing a non C<sub>2</sub>-symmetrical chiral auxiliary and a stereogenic phosphorus center

Racemic  $\alpha$ -chiral aldehydes have been successfully applied in asymmetric HWE-reactions using the strategy of kinetic resolutions.<sup>20,22</sup> With configurationally labile substrates even dynamic kinetic resolutions can be carried out if the base used for the deprotonation of the phosphonate is sufficiently strong to racemize the aldehyde by protonation/deprotonation sequences *via* its enolate.<sup>23</sup> Thus, alkenylation of  $\alpha$ -aminoaldehyde **49** with the phosphonate **50** in the presence of KHMDS/18-crown-6 gave rise to **51** in good yield and selectivity.<sup>23b</sup> The stereochemical outcome of this reaction can be rationalized by a transition state **52**, in which the chiral auxiliary dictates the face of the phosphonate Z(O)-enolate that is attacked, the R groups on the phosphonate dictate the relative configuration between C2 and C3, and finally selection of the aldehyde enantiomer occurs in accordance with the Felkin-Anh model. Support for this model comes from the fact that in this type of kinetic resolutions the other aldehyde enantiomer reacts preferentially under chelating conditions.<sup>24</sup>



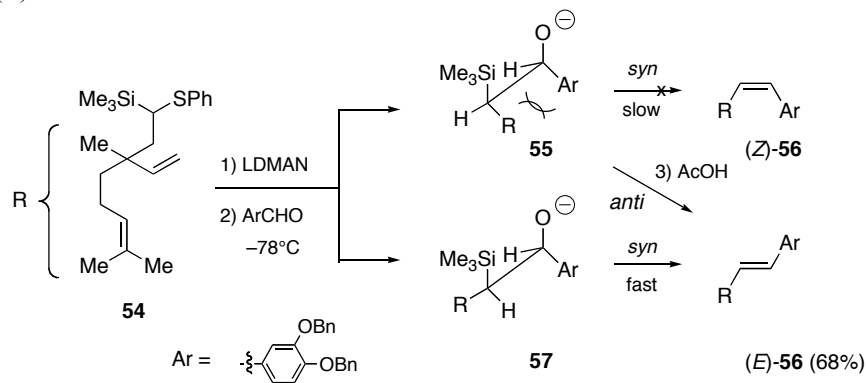
**Scheme 13.** Dynamic kinetic resolution of  $\alpha$ -aminoaldehydes by an asymmetric HWE-reaction

### 13.3. The Peterson Olefination

Conceptually quite similar to the Wittig type reactions but quite different in scope and limitation are alkenylations that proceed through  $\beta$ -

hydroxysilanes, the so-called Peterson olefination. Most commonly, an  $\alpha$ -silylated carbanion is added to a carbonyl compound to give rise to two diastereomeric  $\beta$ -hydroxysilanes, which can be isolated analogous to the previously discussed Horner-Wittig reaction and separately transformed further to alkenes. In distinct contrast, however, by careful control of the reaction conditions either alkene geometry can be obtained from each individual  $\beta$ -hydroxysilane. Under basic conditions, a *syn*-elimination of the silyl and hydroxy group takes place, presumably through a pentacoordinated intermediate, which is formed by attack of the deprotonated oxygen onto silicon. On the other hand, under acidic conditions protonation of the hydroxyl group followed by an E2-elimination occurs, reversing the stereochemical outcome with respect to the base variant.

Based on this mechanistic rationale it is possible to synthesize selectively *E*-alkenes by utilizing the different reaction rates of the diastereomeric  $\beta$ -hydroxysilanes in the elimination step. Upon sulfur-lithium exchange of **54** and reaction with an aldehyde, only **57** undergoes isomerization at low temperature to (*E*)-**56**, while *syn*-elimination of **55** is hampered due to steric hindrance between R and Ar. Subsequent addition of acid then converts **55** in an *anti*-elimination to (*E*)-**56** as well.<sup>25</sup>

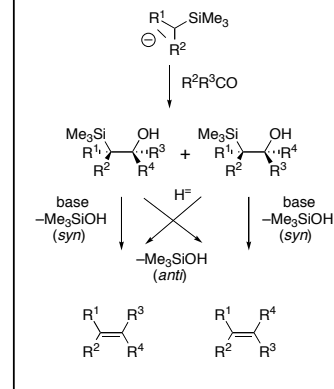


**Scheme 14.** Stereoconvergent Peterson reaction

Many methods have been utilized to generate  $\alpha$ -silyl carbanions, which were subsequently reacted with carbonyl compounds to yield alkenes, but the most valuable strategies are those, which will form  $\beta$ -hydroxysilanes diastereoselectively, thus making their separation or the combination of different work up protocols superfluous in order to arrive at geometrically pure products.

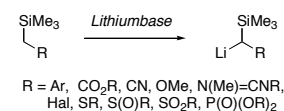
Peterson reagents being stabilized by electron withdrawing substituents such as aldehydes, ketones or esters, preferentially give rise to (*E*)-alkenes upon deprotonation with a lithium base without isolation of the intermediate  $\beta$ -hydroxysilanes. The origin of this stereoselectivity has not been extensively explored, but it appears plausible that similar arguments as previously discussed for stabilized Wittig ylides. For example, in the synthesis of maytansine, the trisubstituted alkene **60** was synthesized as a single diastereomer using **59**, in which the aldehyde functionality is masked as an imine.

**Chart 9.** The Peterson olefination

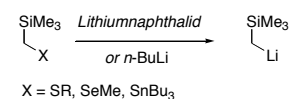


**Chart 10.** Common methods for the generation of  $\alpha$ -silyl carbanions.

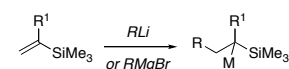
1. Deprotonation

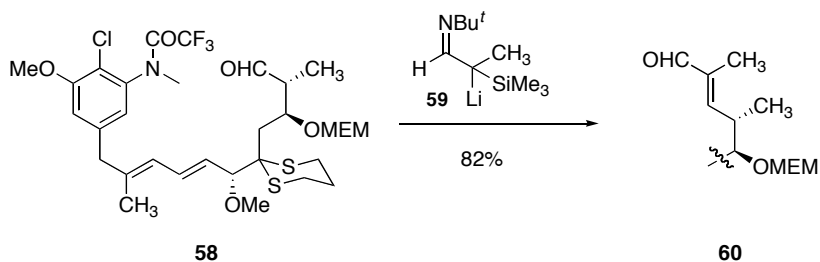


2. Heteroatom Substitution



3. Nucleophile Addition to Vinylsilanes





**Scheme 15.** Stereoselective Peterson olefination in the synthesis of maytansine.

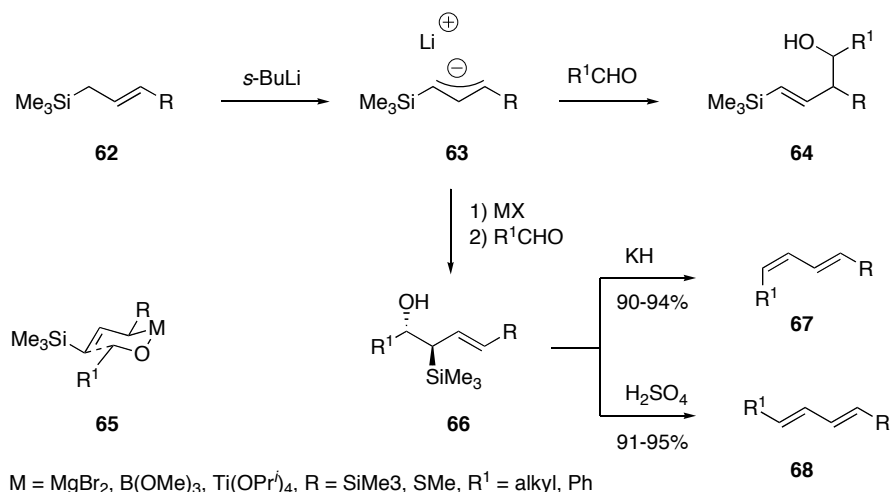
Alternatively, when non-enolizable aldehydes are employed, alkenylation can be induced with fluoride, giving rise to (*E*)-alkenes with high stereoselectivity.<sup>26</sup>

In contrast, *N,N*-dibenzyl-(triphenylsilyl)acetamide has been reported to yield with high selectivity (*Z*)-alkenes upon metallation with LDA followed by reaction with aromatic aldehydes.<sup>27</sup>



**Scheme 16.** Stereoselective synthesis of (*Z*)-configured  $\alpha,\beta$ -unsaturated amides.

Allyltrimethylsilanes **62** can readily be deprotonated with *s*-BuLi, however, upon reaction with an aldehyde 4-hydroxy-1-alkenylsilanes by attack on the  $\gamma$ -position in **63** and not Peterson products, which would require attack on the  $\alpha$ -position are often obtained. However, transmetallation of lithium by titanium, boron or magnesium changes the regioselectivity to the  $\alpha$ -position, and moreover, *anti*  $\beta$ -hydroxysilanes are obtained with high diastereoselectivity, which is best explained by a Zimmerman-Traxler type transition state model. Acid or base induced elimination can then be carried out to yield either *Z,E* or *E,E*-dienes.



Scheme 17. Stereoselective synthesis of 1,3-dienes

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