B Olefination using Main Group Elements

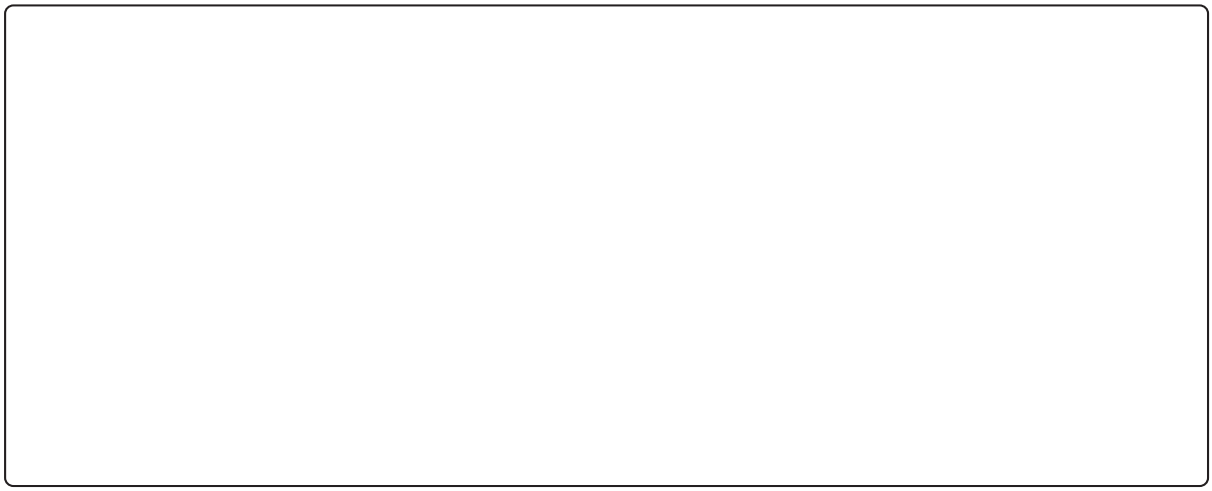
Objectives:

By the end of this set of lectures you will:

1) be able to use P and Si reagents for constructing double bonds from aldehydes and ketones.
2) have an understanding of the mechanisms of these reactions and appreciate how they affect the stereoselectivity of the processes.

Methods of Olefination

A possible disconnection:

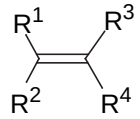


Selectivity Issues:

Chemoselectivity – which types of carbonyl group are reactive (relative reactivity also important).

Stereoselectivity – olefins can exist as (*E*)- or (*Z*)-stereoisomers; need to be able to control the stereochemical outcome of olefination reactions in a predictable fashion.

Stereochemical Notation:

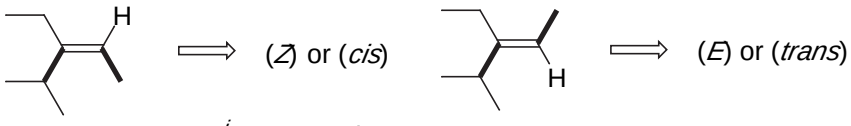


Generally: use CIP rules to assign priorities to each end of the double bond.

If $R^1 > R^2$ and $R^3 > R^4$ then olefin is assigned (*Z*) (zusammen)

If $R^1 > R^2$ and $R^4 > R^3$ then olefin is assigned (*E*) (entgegen)

An example:



^{i}Pr > Et and Me > H

B.1 Phosphorus Reagents in Olefination

B.1.i Wittig Reaction

- *Chemoselectivity*: ylide reactive towards all types of aldehydes and ketones (aldehydes much more reactive than ketones). Generally NO reaction with nitriles, esters, amides, nitro groups *etc*.

- *Regioselectivity*: α,β-unsaturated aldehydes/ketones react exclusively in a 1,2-fashion; *i.e.* at the C=O, not at the C=C.

- *Stereoselectivity*: dependent on a variety of factors (most importantly the type of ylide) but some general rules are available for predicting the stereochemical outcome of the reaction (see later).

Formation of Phosphonium Ylide Reagents

Phosphonium ylides are readily prepared by treating the corresponding phosphonium salt with an appropriate base. The ylides are usually used directly although 'stabilised' ylides are sufficiently stable that they can often be isolated; indeed some are commercially available *e.g.* $Ph_3P{=}CHC(O)Me$.

Formation of Phosphonium salts

S_N2-substitution of alkyl halide with a phosphine (phosphines are very good nucleophiles):

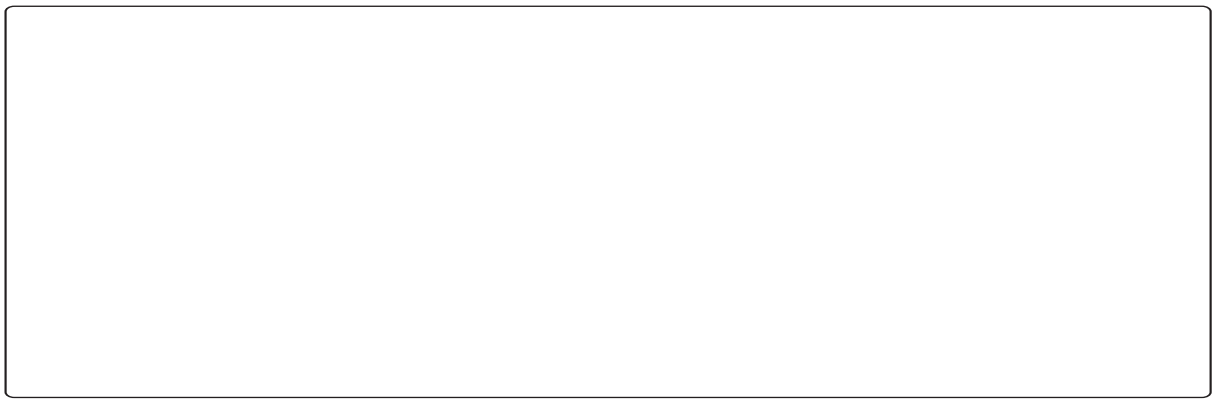
Reaction proceeds best with those alkyl halides that most readily undergo S_N2-reactions:

- For activated RX (primary, benzylic halides with X = Br or I): $CHCl_3$ or THF / 50 °C.

- For branched alkyl halides and if X = Cl, need to go to elevated temperatures (*e.g.* use toluene (b.p. 111 °C), xylene (b.p. 140 °C)) or fuse reagents (*i.e.* use no solvent and just heat).

Ylide Formation

Q: What base to use? A: Depends on the substituents.



The phosphonium group has a strong anion stabilising effect.

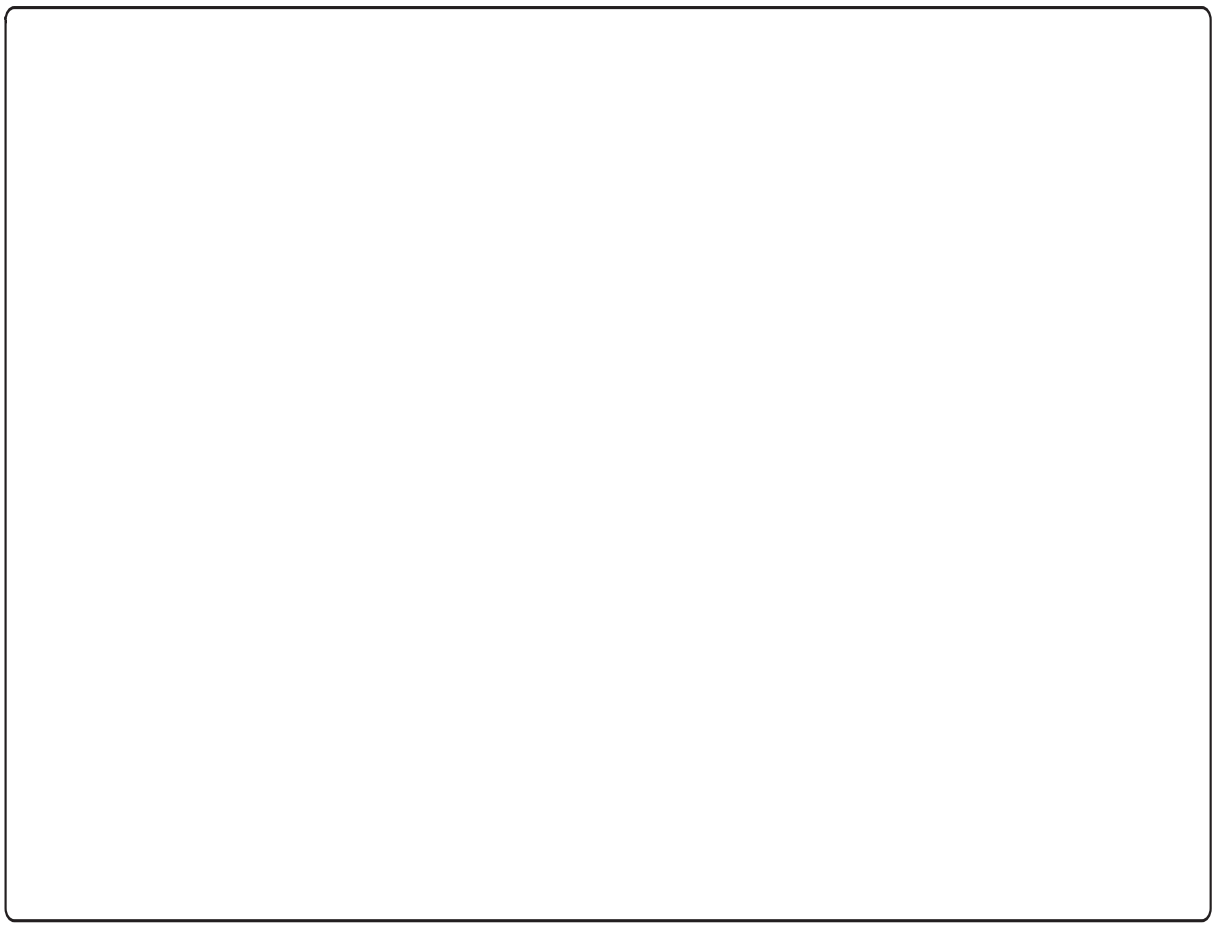
Alkyltriphenylphosphonium salts can be deprotonated with bases such as alkoxide (pK_a ROH = 16-18), NaH and KH, although strong bases like n-BuLi (pK_a BuH = 42), MetHMDS (Met = Li, Na, K), LDA (pK_a $^{i}Pr_2NH$ = 38), and $NaNH_2$ (pK_a NH_3 = 36) are more frequently used.

The presence of additional anion-stabilising groups (*e.g*. SO_2R, CO_2R, CN) allows much milder bases to be used such as $NaHCO_3$ (pK_a H_2CO_3 = 6).

If LiX salts are NOT formed during the metallation step (*i.e*. if Na or K bases are used to form the ylide), the reaction is said to be conducted under **'salt-free' conditions**.

Ylide Classification

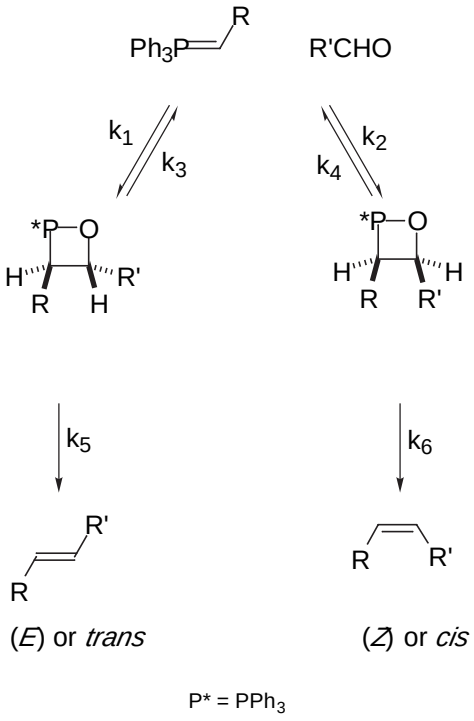
Phosphonium ylides can be divided into three general categories according to their substitution pattern. The stereoselectivity of the olefination reaction is different for each class (BIG generalisation).



Reaction of Non-Stabilised Ylides with Aldehydes – Mechanism

The observation that non-stabilised ylides react with aldehydes to provide the less thermodynamically stable (*Z*)-olefin has prompted detailed mechanistic studies to try and account for this unusual selectivity.

The currently accepted mechanism for the reaction of non-stabilised ylides with aldehydes *under 'salt-free' conditions* (*i.e.* in the absence of soluble metal salts) is outlined below:



P* = PPh_3

Notes:

1. The reaction is under **KINETIC** control (thermodynamically controlled Wittig reactions of any type are very unusual); normally $k_2 > k_1$ and $k_5 \approx k_6$ so assuming the rate of the reverse reaction (*i.e.* k_3 and k_4) is negligible, the (*Z*)-olefin predominates.

2. The mechanism that was initially proposed by Wittig and others involved an aldol-like addition to give betaine intermediates, which then formed the oxaphosphetanes (*i.e.* a two-step process). *Under salt-free conditions*, there is **no** evidence for betaine formation whereas the intermediate oxaphosphetanes have been observed using low temperature ^{1}H- and ^{31}P-NMR studies suggesting these four-ring intermediates are formed directly through a [2+2]-like cycloaddition.

3. Oxaphosphetane formation is best viewed as an asynchronous cycloaddition, as is its collapse to the olefin product (this latter step is a *stereospecific* process *i.e*. *cis* oxaphosphetane→ (*Z*)-olefin; *trans* oxaphosphetane→ (*E*)-olefin).

4. Without a retro-Wittig process (*i.e.* a reversible first step), the stereoselectivity of the initial cycloaddition should determine the (*E/Z*)-olefin ratio. The ratio of oxaphosphetanes can be measured by trapping these intermediates at low temperature (< -80 °C) with anhydrous HBr and isolating the corresponding β-hydroxyphosphonium salts. When this is done, the observed ratio of β-hydroxyphosphonium salts - and therefore of *cis* and *trans* oxaphosphetanes - usually does not reflect exactly the stereoselectivity of the final olefin products that would have been formed had the Wittig reaction been allowed to proceed to completion. This suggests that there is a degree of equilibration between these intermediates.

Equilibration is possible by a retro-cycloaddition/cycloaddition process and will favour the thermodynamically more stable *trans* oxaphosphetane. Futhermore, erosion of stereoselectivity is worsened by $k_4 > k_3$. This type of process is known as *stereochemical drift*.

The (*Z*)-selectivity is therefore not only affected by the stereoselectivity of the initial cycloaddition, but also by the degree of equilibration.

A variety of factors affect the stereoselectivity of the cycloaddition and the degree of equilibration. These include: cation, anion, solvent, temperature, concentration, carbonyl compound and substituents on the phosphine.

Lithium salts

The presence of Li salts not only reduces the *cis/trans* selectivity of the initial cycloaddition but also facilitates the retro-cycloaddition. Other metal halides soluble in organic solvents can also erode the (*Z*)-stereoselectivity.

Ligands on phosphorus

Triphenylphosphonium ylides give better (*Z*)-selectivity than trialkylphosphonium ylides.

Optimum conditions for achieving high (*Z*)-selectivity with non-stabilised ylides

1. salt-free conditions *i.e.* use Na or K bases to prepare the ylide;
2. use $Ph_3P{=}CHR$, not $R^1{}_3P{=}CHR$ (R^1 = alkyl group);
3. non-protic, polar solvent *e.g.* THF, ether, DME;
4. avoid sterically encumbered substituents on both aldehyde and ylide;
5. maintain a low temperature for oxaphosphetane formation (< -75 °C).

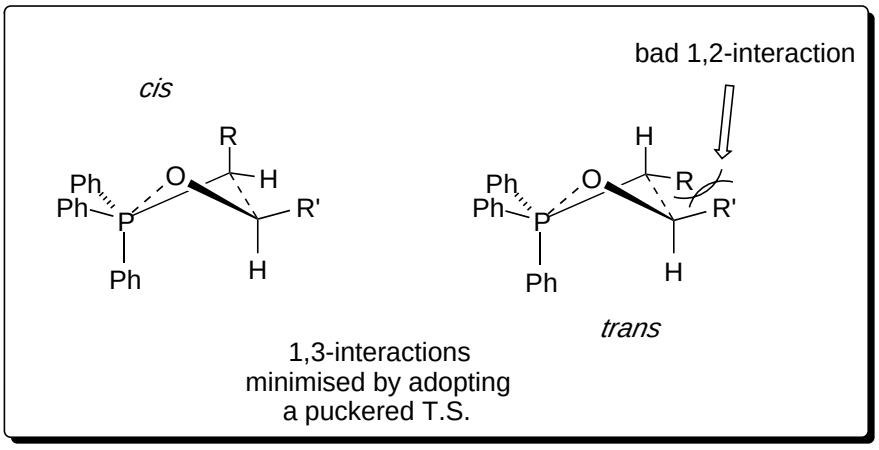
see: M. Schlosser, B. Shaub, J. de Oliveira-Neto, S. Jeganathan, *Chimia*, 1986, **40**, 244-245.

Origins of Stereoselectivity using non-stabilised ylides under salt-free conditions

To summarise so far: the Wittig reaction is under *kinetic control*; the *cis* oxaphosphetane is formed *stereoselectively* under salt-free conditions, and decomposes in a *stereospecific* fashion to provide the (*Z*)-olefin product.

Therefore we require T.S.s which differentiate between the *cis* and *trans* oxaphosphetane isomers. Extensive work by Vedejs and co-workers has provided plausible transition states:

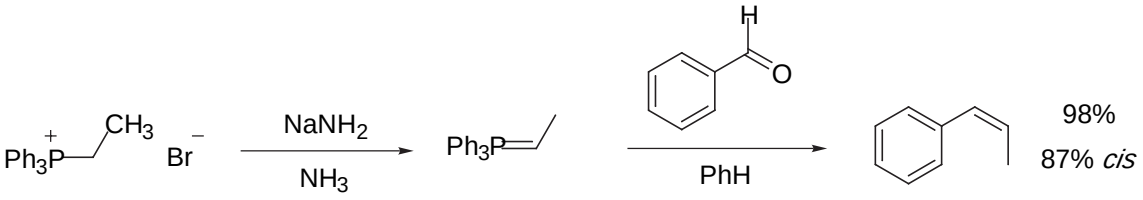
They propose an early (*i.e*. more closely resembling starting materials) 4-centre cyclic T.S. in which the 4-membered ring is ***puckered*** *to minimise unfavourable interactions between the phosphorus substituents and the substituents at the aldehyde and ylide centres.*

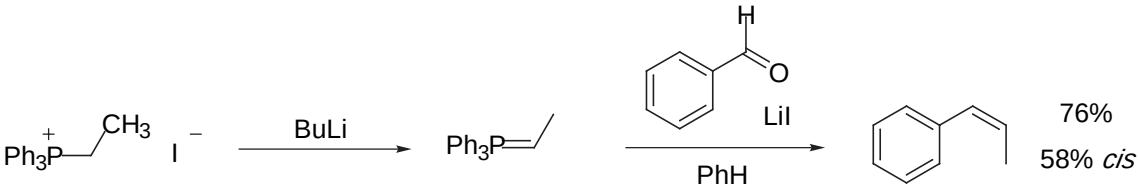


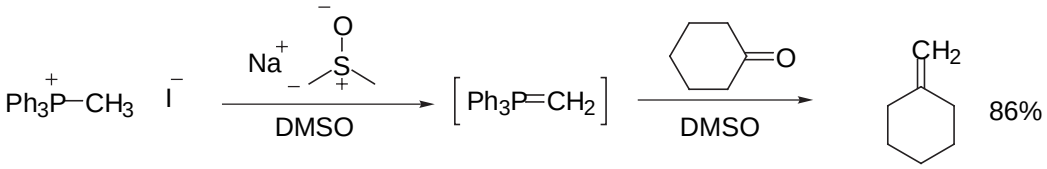
Key references:

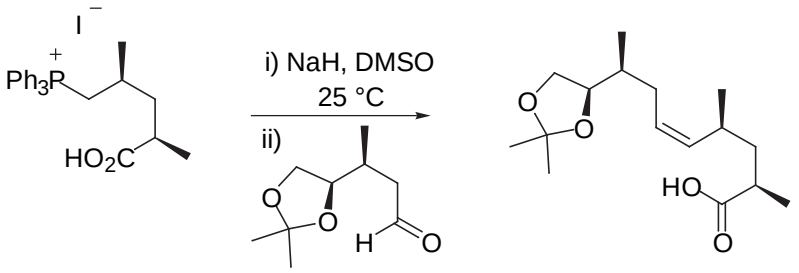
E. Vedejs, G. P. Meier, K. A. J. Snoble, *J. Am. Chem. Soc*., 1981, **103**, 2823-2831.
E. Vedejs, C. F. Marth, R. Ruggeri, *J. Am. Chem. Soc*., 1988, **110**, 3940-3948.
E. Vedejs, C. F. Marth, *J.Am. Chem. Soc*., 1988, **110**, 3948-3958.

Some Examples

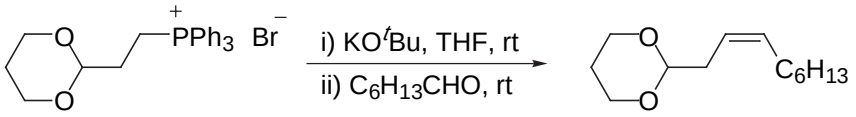








70% (+ 20% *trans* isomer)



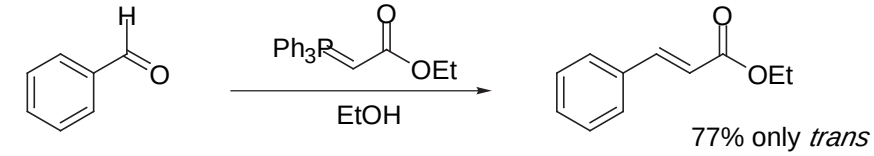
72%, only (*Z*)-isomer

Stabilised Ylides

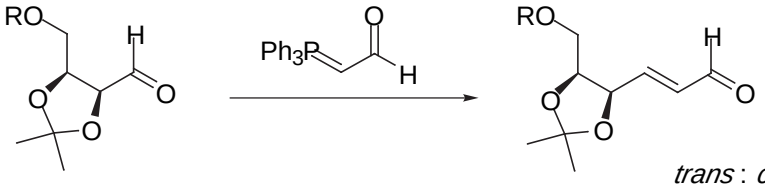
The mechanism involving stabilised ylides, *i.e*. those containing an anion-stabilising group α-to the ylide carbon has been less well studied since the intermediates in the reaction are very short-lived.

The reaction is again under **kinetic control** with the product-determining step as before being the reaction of the ylide with the aldehyde to form an oxaphosphetane intermediate. In contrast to non-stabilised ylides, stabilised ylides usually provide the thermodynamically more stable (*E*)-olefin.

Examples



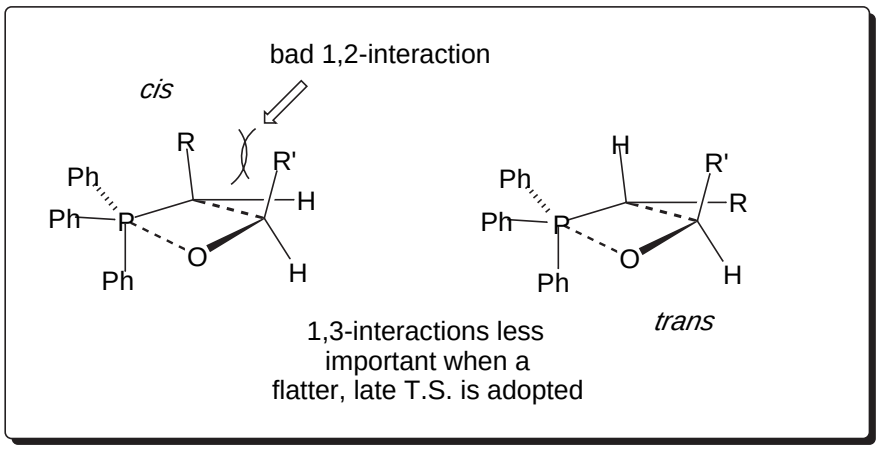
77% only *trans*



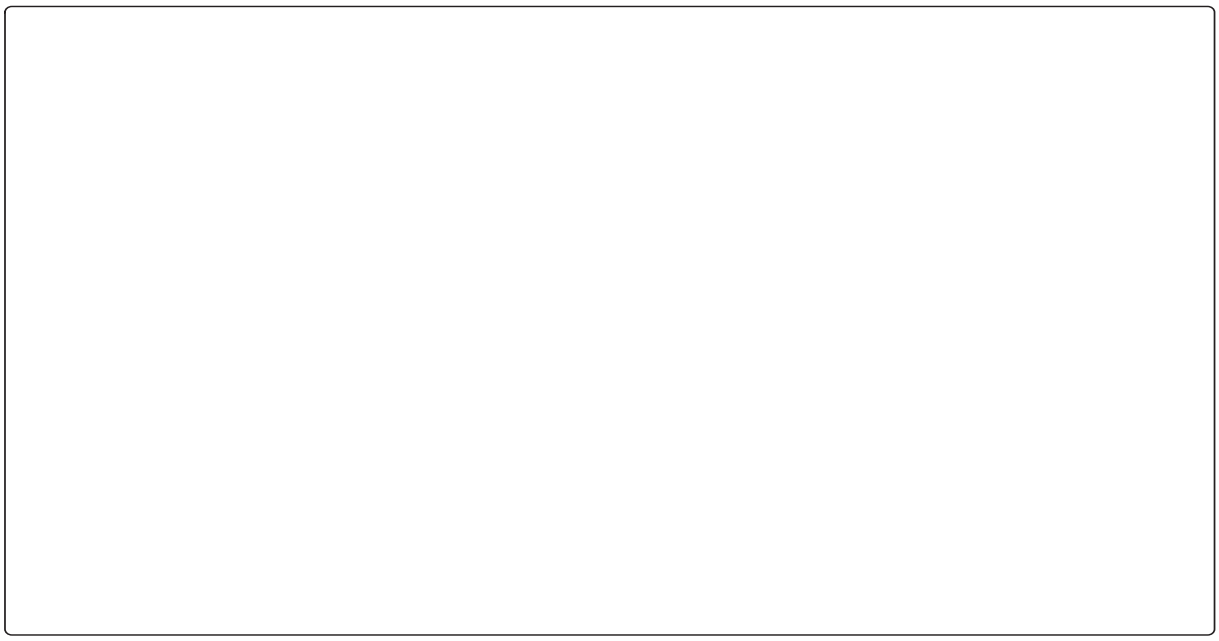
trans : *cis* >20:1

R = $CHPh_2$

To account for this difference, Vedejs and co-workers have proposed that the formation of the oxaphosphetane proceeds through a later T.S. (i.e. resembling the product) where the phosphorus more closely adopts a trigonal bipyramidal structure. This generates a flatter 4-membered T.S. where 1,3-interactions (between the substituents on the P and the aldehyde) are less important; minimising 1,2-interactions are again responsible for controlling the *cis/trans* selectivity of the oxaphosphetane.

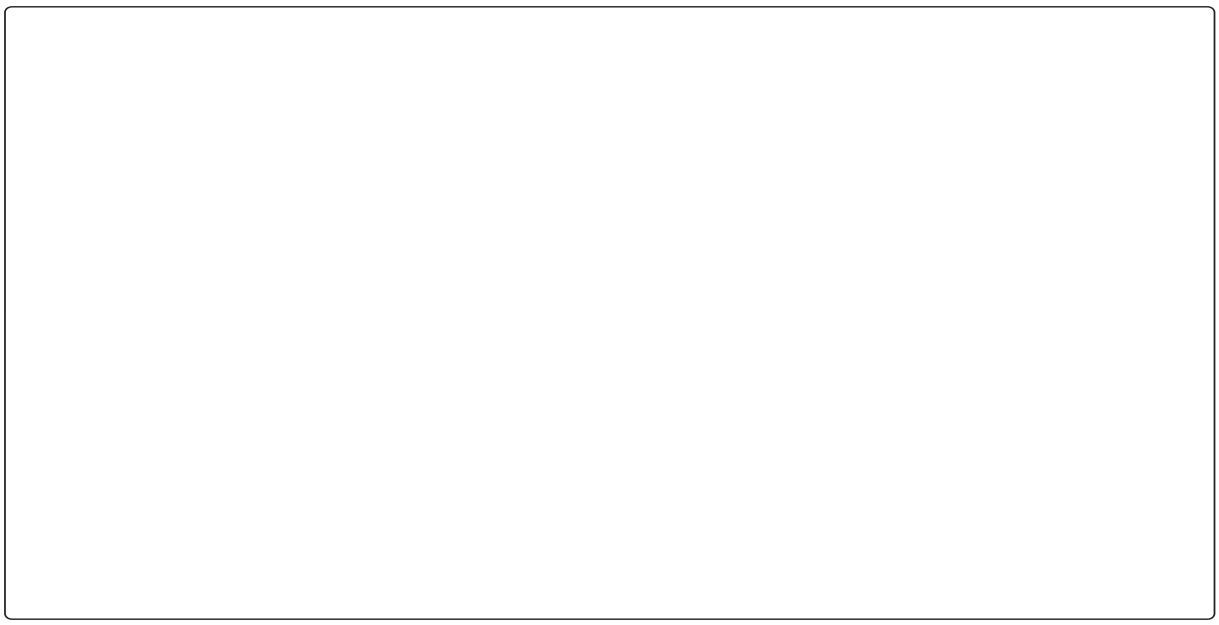


B.1.ii Horner-Wadsworth-Emmons Reaction



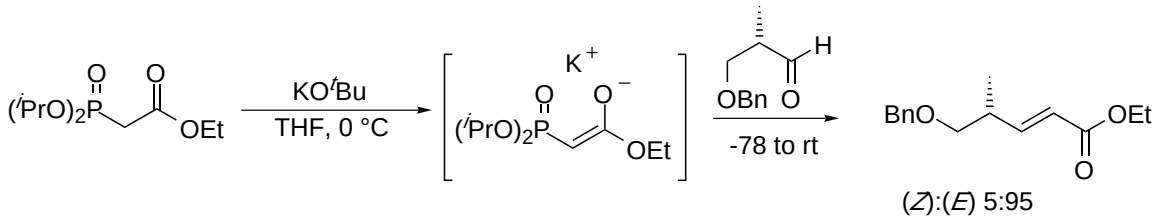
Formation of Phosphonates

Arbusov reaction:



Very general reaction and easy to carry out. Heat the phosphite and alkyl halide (usually bromides) in the absence of solvent. $(MeO)_3P$ or $(EtO)_3P$ are most convenient since the alkyl halide by-product (MeBr or EtBr respectively) is volatile and easy to remove.

Example



Notes:

1. The driving force of the reaction is once more formation of a P=O double bond.

2. The reaction only works well with phosphonates that possess an α-anion-stabilising substituent – no such restriction with the Wittig reaction.

3. α-Phosphonate anions are more nucleophilic than phosphonium ylides (pentavalent P cannot stabilise charge as well). This means we can often use less reactive aldehydes and ketones and employ milder reaction conditions.

4. Typical bases: NaH, KH, alkoxides, $NaNH_2$; wide range of solvents from PhH and toluene to ethers, THF and DMSO.

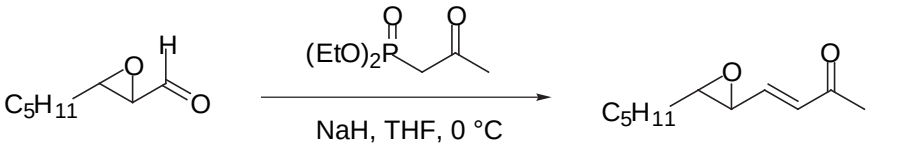
5. The phosphonic acid salt by-product is water-soluble greatly facilitating work-up.

Mechanism:

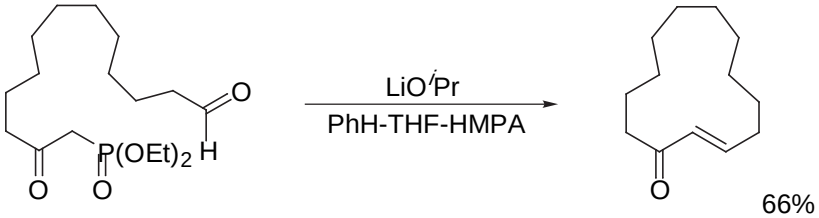
The reaction has been less well studied than the Wittig reaction; it follows a similar pathway to the so-called Horner-Wittig reaction in which a betaine-like intermediate precedes the oxaphosphetane; the intermediate β-hydroxy phosphonates are occasionally isolable.

The stereoselectivity is again determined by the initial condensation reaction and the degree of equilibration. The stereoselectivity of the addition event can often be modulated by varying the alkoxy substituents on the phosphonate. *Methyl phosphonates sometimes give relatively low stereoselectivity often favouring the (Z)-olefin. Change to bulkier groups such as Et or even better ^{i}Pr groups and excellent (E)-selectivity is often observed.*

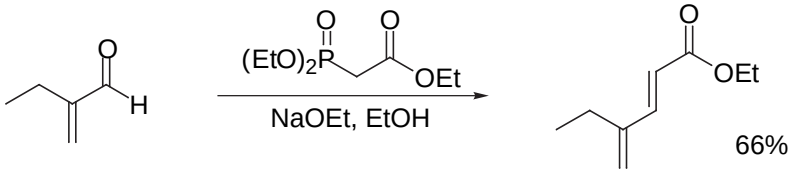
Some Examples



78% *trans* : *cis* > 20:1



66%



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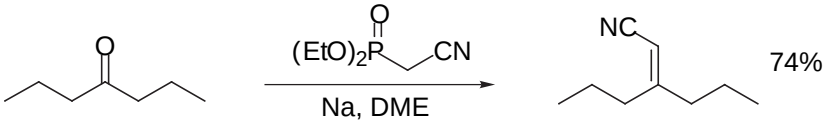
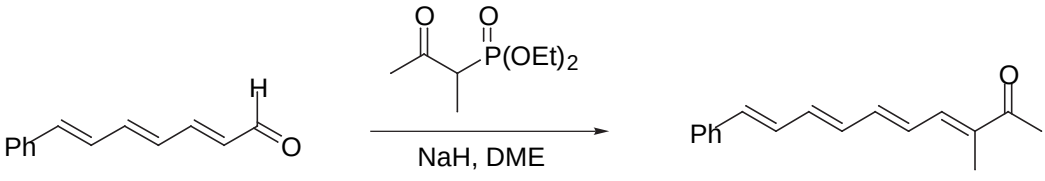


74%



(*E, E, E, E*)

Summary

- Phosphorus ylides are the most important reagents for forming double bonds from aldehydes and ketones.

- The phosphorus atom has a relatively strong stabilising effect on α-carbanions. This can be attributed to electron donation into vacant relatively low lying 3d AOs on the phosphorus atom and through the formation of induced dipoles arising from polarisation of the relatively large electron cloud about the phosphorus nucleus.

- Although the reactions of phosphorus ylides (Wittig) and phosphonium ylides (Horner-Wadsworth-Emmons) with carbonyl groups are under kinetic control, the formation of a strong P=O bond provides an important thermodynamic driving force for the reaction.

- In the case of Wittig reagents, 'stabilised' ylides provide (*E*)-olefins whereas 'non-stabilised' ylides afford the thermodynamically less stable (*Z*)-olefins. This is a big generalisation and only applies to 'salt-free' reaction conditions.
  - The stereoselectivity can be rationalised by *stereoselective* formation of an intermediate oxaphosphetane and subsequent *stereospecific* collapse to the corresponding olefin.
  - The presence of Li salts opens up pathways which allow equilibration of the oxaphosphetane intermediates. This serves to erode the (*Z*)-selectivity in the case of 'non-stabilised' ylides.

- Horner-Wadsworth-Emmons reactions only work well with phosphonates which also contain anion-stabilising substituents.
  - (*E*)-olefins are generally produced.
  - The phosphonic acid salt by-product is water-soluble which facilitates work-up (compare this with the triphenylphosphine oxide by-product in Wittig reactions which can be difficult to separate from the desired product).