**Solvent Free Wittig Reactions**

adapted from Nyugen and Weizman, J. Chem. Educ. 2007, 119.

*The Wittig reaction: background and mechanistic considerations*
The Wittig reaction is extensively used in organic synthesis for the construction of double bonds. The reaction occurs between a carbonyl group (an aldehyde or a ketone) and an ylide. Ylides are organic phosphorus compounds with a formal double bond between phosphorus and carbon (Scheme 1). The byproduct of the reaction is triphenylphosphine oxide and the formation of a strong phosphorous-oxygen bond drives the reaction forward. The reaction is very popular because of its simplicity, high efficiency and high stereoselectivity. The importance of the Wittig reaction was recognized by the Nobel Prize committee in 1979.
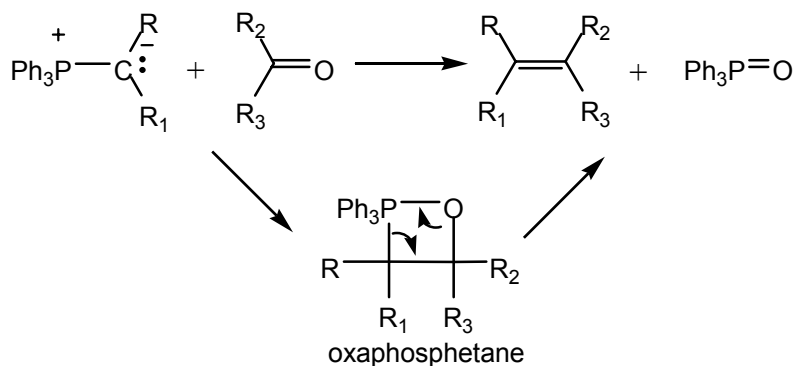

Scheme 1: The Wittig reaction

The proposed mechanism of the reaction involves the formation of a four-membered cyclic intermediate (oxaphosphetane) which subsequently collapses to give the products. There are two possible routes leading to the formation of the oxaphosphetane. The first involves nucleophilic attachment of the negatively charged carbon of the ylide onto the polarized carbonyl group. This leads to the formation of a dipolar ion (zwitterion) known as betaine. Following this is the intramolecular ring closure that gives the oxaphosphetane (Scheme 2, I). Alternatively, the ring can be formed by concerted [2+2] cycloaddition (Scheme 2, II). Such addition mechanisms explain the stereochemical outcome of the Wittig reaction.
There is no direct experimental evidence to support the formation of betaine during the reaction. When lithium salts are added to Wittig reactions, it is possible to isolate stable complexes between the salt and a betaine. Nevertheless, uncomplexed betaines were never observed by NMR. Since betaines have not been directly observed and the concerted addition supports the observed stereoselectivity, the cycloaddition mechanism is currently the accepted model.
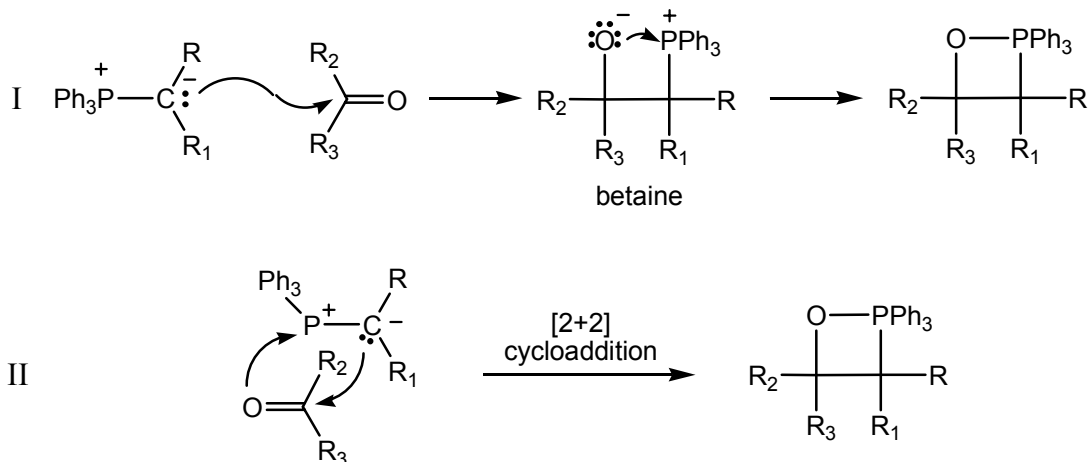
Scheme 2. Alternative routes for the formation of oxaphosphetane

Ylides are prepared from the corresponding alkyl halides by displacement of the halide with trialkyl phosphine (Scheme 3). Since the proton alpha to the phosphorous is relatively acidic, subsequent treatment with base produces the ylide. Usually the ylides are prepared just before the reaction.
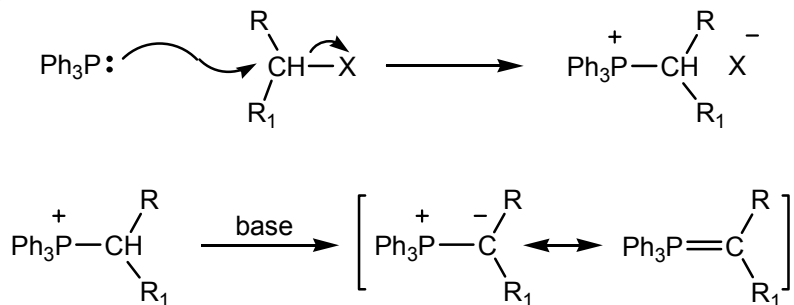

Scheme 3. Prepartion of ylides.

Various alkyl halides require bases of different strengths. For example:
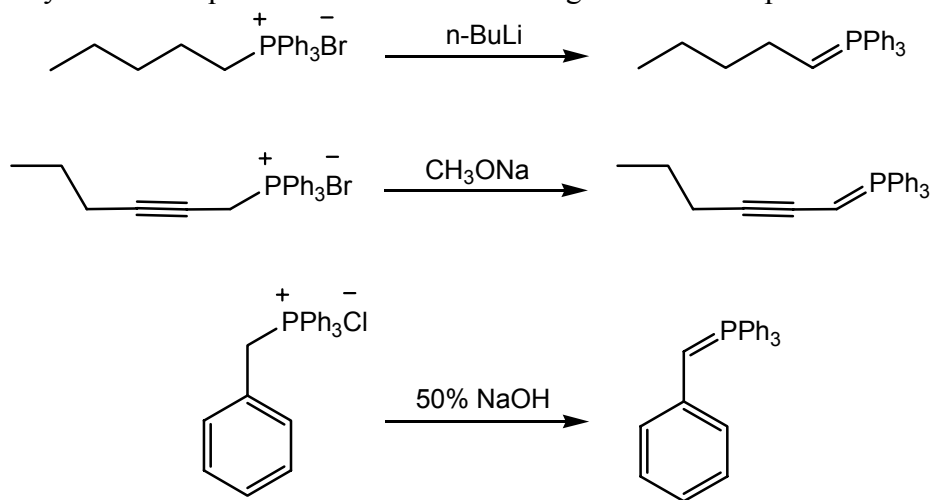
Explain this trend. What can you say about the stability of the corresponding ylides?

The experiment

In the following lab you will synthesize two compounds using the Wittig reaction and then analyze the products by ^{1}H NMR. We will be using a commercially available ylide which of course indicates a high stability of this ylide. Use resonance structures to explain the origin of this high stability.
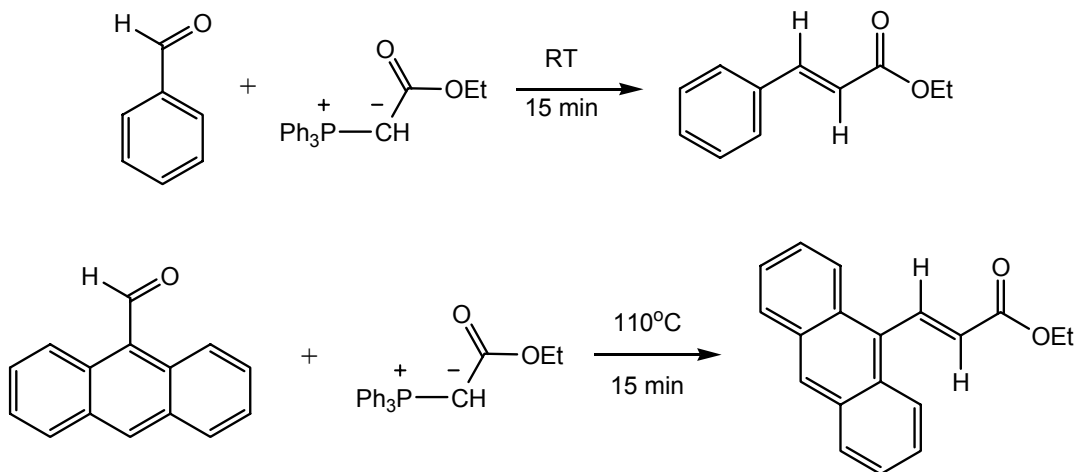
Solvent-free reactions
Unlike most reactions that you have previously encountered, the following reactions are done without addition of solvent. Although organic solvents are very useful for dissolving compounds and providing a medium for those compounds to react, they also impose health and environmental risks. Therefore minimizing or avoiding solvents in organic synthesis reduces hazards and waste. Solvent-free reactions typically have at least one compound in a liquid form acting as a semi-solvent. In this experiment the first reaction uses a liquid aldehyde and the reaction occurs in the interface between the solid and liquid. The second reaction is between two solids but, after heating, one of the solids melts to provide the liquid component.

Hazards and disposal
Hexanes and methanol are flammable liquids. Other reagents are potentially irritants. Dispose of all solids in the appropriate labeled container.

Experimental procedure

Synthesis of Ethyl trans-Cinnamate
Weigh 201 mg (0.57 mmol) of (carbethoxymethylene)triphenylphosphorane into a 3 mL conical vial. Add 50.8 µL of benzaldehyde (0.5 mmol) and a magnetic spin vane. Stir the mixture for 15 minutes at room temperature. Add hexanes (3 mL) and continue stirring for a few minutes. Remove the solvent from the solid (what is the solid?) using a filtering pipette:
Prepare a filtering pipette with a small plug of cotton near the tip of the pipette. Place the pipette into the vial and draw the top liquid into the pipette. Transfer the liquid into a

clean pre-weighed vial. Insert the pipette again into the original vial, this time placing the tip of the pipette flush against the conical bottom. Draw the remaining liquid and transfer it to the vial (the cotton plug will prevent transferring the solid). Add a new portion of hexanes (3 mL) and repeat the process. Combine the solution with the previous hexanes solution. Evaporate the solvent using evaporator or a Hickman still head. If a solid is observed during the evaporation, you will need to filter the solution through a filtering pipette and evaporate again.

Weigh the product and calculate the yield. Analyze your product by TLC and m.p.

Synthesis of E-3-(9-Anthryl)-2-propenoic acid ethyl ester

Heat a sand bath to 120 $^{\circ}$C over a stirring hot plate.

Weigh 103 mg (0.5 mmol) of 9-anthraldehyde and 184 mg of (carbethoxymethylene)triphenylphosphorane (0.5 mmol) into a 3 mL conical vial. Add a magnetic spin vane and cap the vial. Insert the vial into the preheated sand bath. Once the solid is melted, continue the stirring for an additional 15 minutes. Remove the vial from the sand bath and let it cool to room temperature.

Add hexanes (3 mL) and continue stirring for a few minutes. Remove the solvent from the solid via a filtering pipette as before. Transfer the liquid into a clean pre-weighed vial. Add a new portion of hexanes (3 mL) and repeat the process. Combine the solution with the previous hexanes solution. Evaporate the solvent using an evaporator or a Hickman still head. Recrystallize the yellowish oil from hot methanol (1 mL) using a Craig tube.

Weigh the product and calculate the yield. Prepare a sample for NMR in $CDCl_3$.

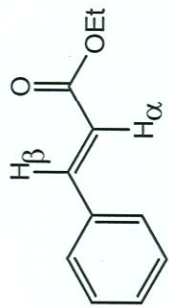### Post lab data analysis

Part a: analyzing the NMR spectrum of ethyl cinnamate

Before starting to analyze the spectrum think about the following aspects of the Wittig reaction of a stabilized ylides. How many products can be obtained in a Wittig reaction? Are stabilized ylides special with respect to the product distribution? What is the byproduct of the reaction? Is it present in the spectrum?

The Wittig reaction yields a mixture of *E* and *Z* isomers. Stabilized ylides (carrying electron withdrawing groups) usually show preference for the formation of the *E* isomer. In this spectrum we have major and minor isomers. Annotate each peak that belongs to the major component with the letter **a,** and each peak of the minor component with the letter **b**. First try to assign the major component. The key point for assigning the ^{1}H spectrum is identifying the two alkenyl protons. Where would you expect to find these protons? Does the integration fit? Notice that this is a non-symmetric double bond and therefore the two protons will have different chemical shifts. Once you have located one proton, measure the coupling constant and use it to locate the second proton.

Which isomer is the major product? How do you assign the configuration based on coupling constants? Now locate the alkenyl protons of the minor component and assign the configuration of this isomer. Is it clear which isomer it is based on coupling constants?

Once you have identified both isomers, calculate the ratio between *E*/*Z* based on integration.

^{1}H NMR, 400 MHz, CDCl$_3$