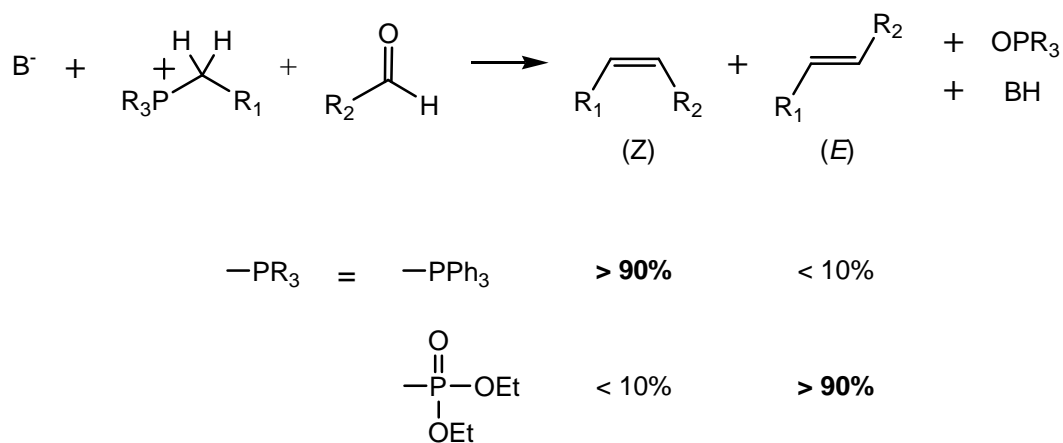


Workshop 7

The Wittig reaction is a useful method for synthesizing di-substituted olefins from two mono-substituted precursors. The general reaction is shown below:

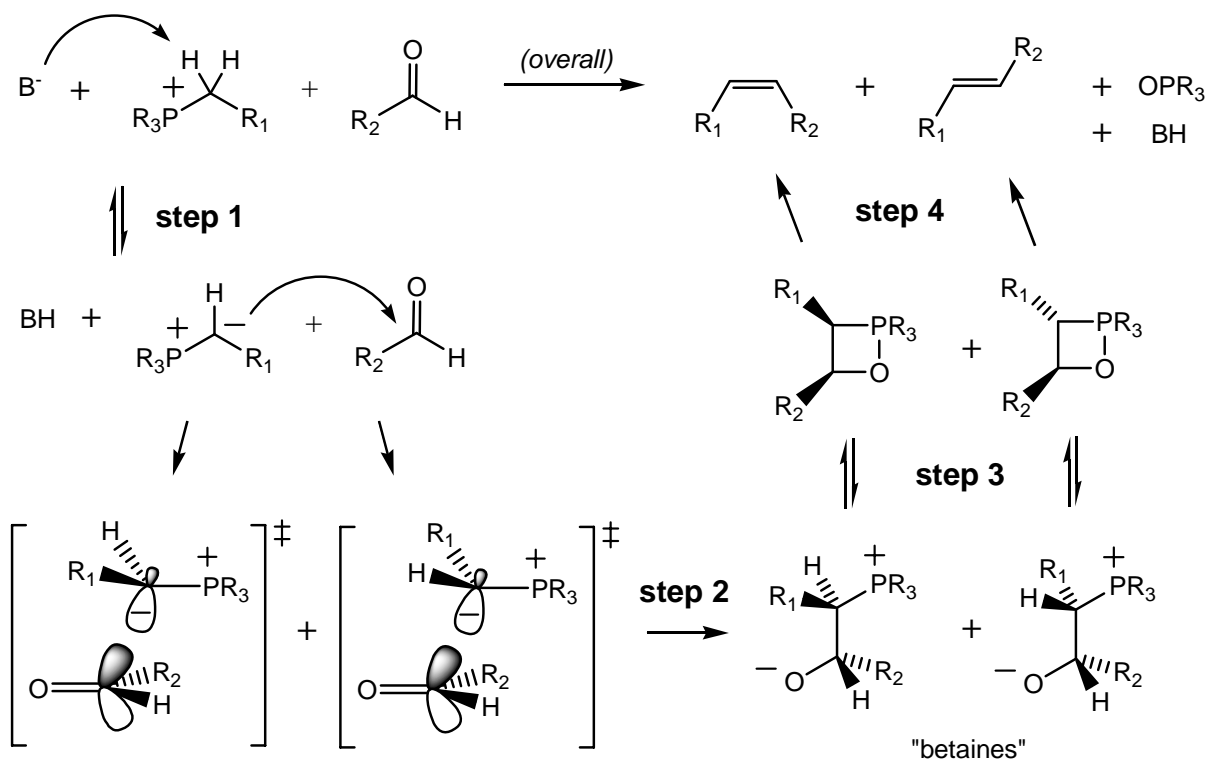


As this scheme shows, one of the interesting features of the Wittig reaction is that it can be used to selectively synthesize either *Z*-(*cis*-) or *E*-(*trans*-)olefins, depending on the phosphine used as the precursor. Selective synthesis of the *Z*-product (for R = Ph) is particularly useful because this (*cis*-)olefin is thermodynamically less stable than the *E*-(*trans*-)olefin, especially when R₁ and R₂ are bulky.

The mechanism shown on the next page has been proposed for the Wittig reaction.¹ Features to note:

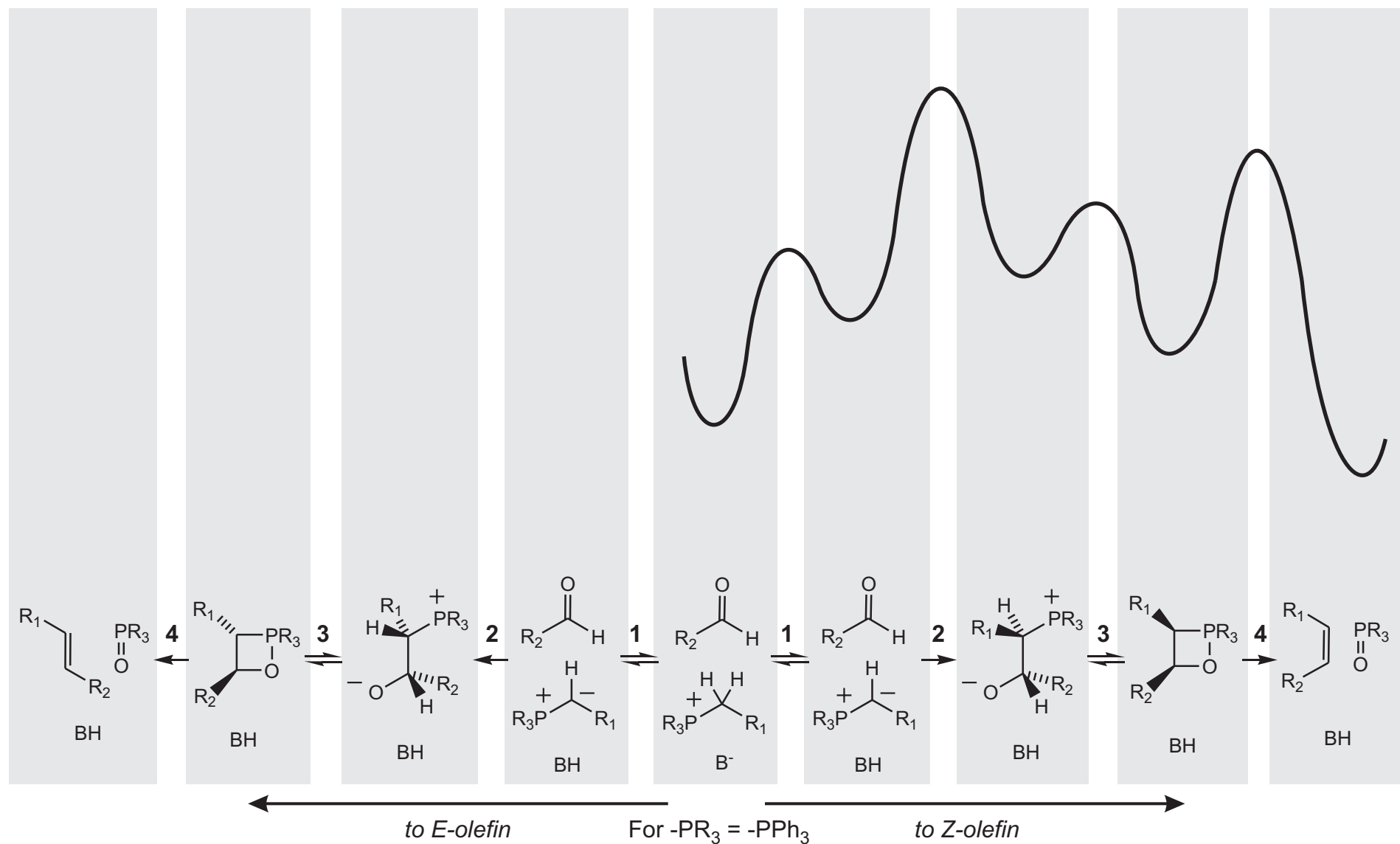
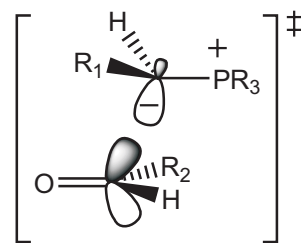
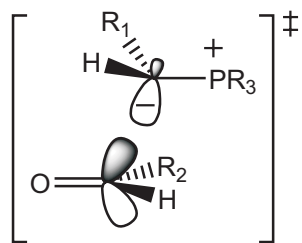
- Steps 1 and 3 are fast. Step 1 is typically performed with a weak base (B⁻), such that it is endothermic.
- Step 2 is slow and endothermic, and generates two “betaine” intermediates whose stereochemistries are determined by the approach of the phosphine and aldehyde in the transition state. This stereochemical difference, in essence, splits the mechanism in two to produce the two different olefin products.
- Step 4 is slow, but quite exothermic.
- Steric interactions between R₁ and R₂ play a major role in determining the relative energies of all intermediates and transition states.

¹ The diagram shows that the phosphine and carbonyl are oriented *anti*- to one another. An alternative mechanistic explanation of the Wittig reaction involves a formal [2+2], *syn*-addition of the reactants. I find it harder to explain the selectivity of the reaction in terms of those transition states, so I've chosen this *anti*- set. The actual structures of the transition states for the Wittig reaction are still the subject of debate.

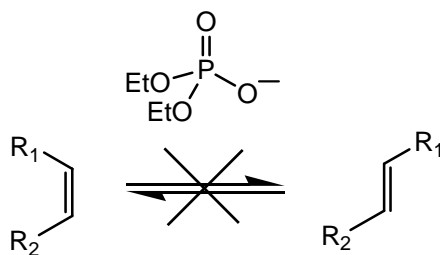


a. It has been proposed that, for $-\text{PR}_3 = -\text{PPh}_3$, selective formation of *Z*-(*cis*-)olefin is determined by the relative energies of the transition states in step 2. Looking at the structures of these transition states above, does this make sense? What about these two transition states would make them different in energy?

b. On the next page, a potential energy diagram for the (preferred) formation of *Z*-olefin for $-\text{PR}_3 = -\text{PPh}_3$. Complete the other half of the diagram for the *E*-olefin. Make sure that the relative intermediate and transition-state energies are consistent with the product selectivity observed. (The gray boxes are there to help you line things up better. I'd advise using pencil for this rather than pen.)



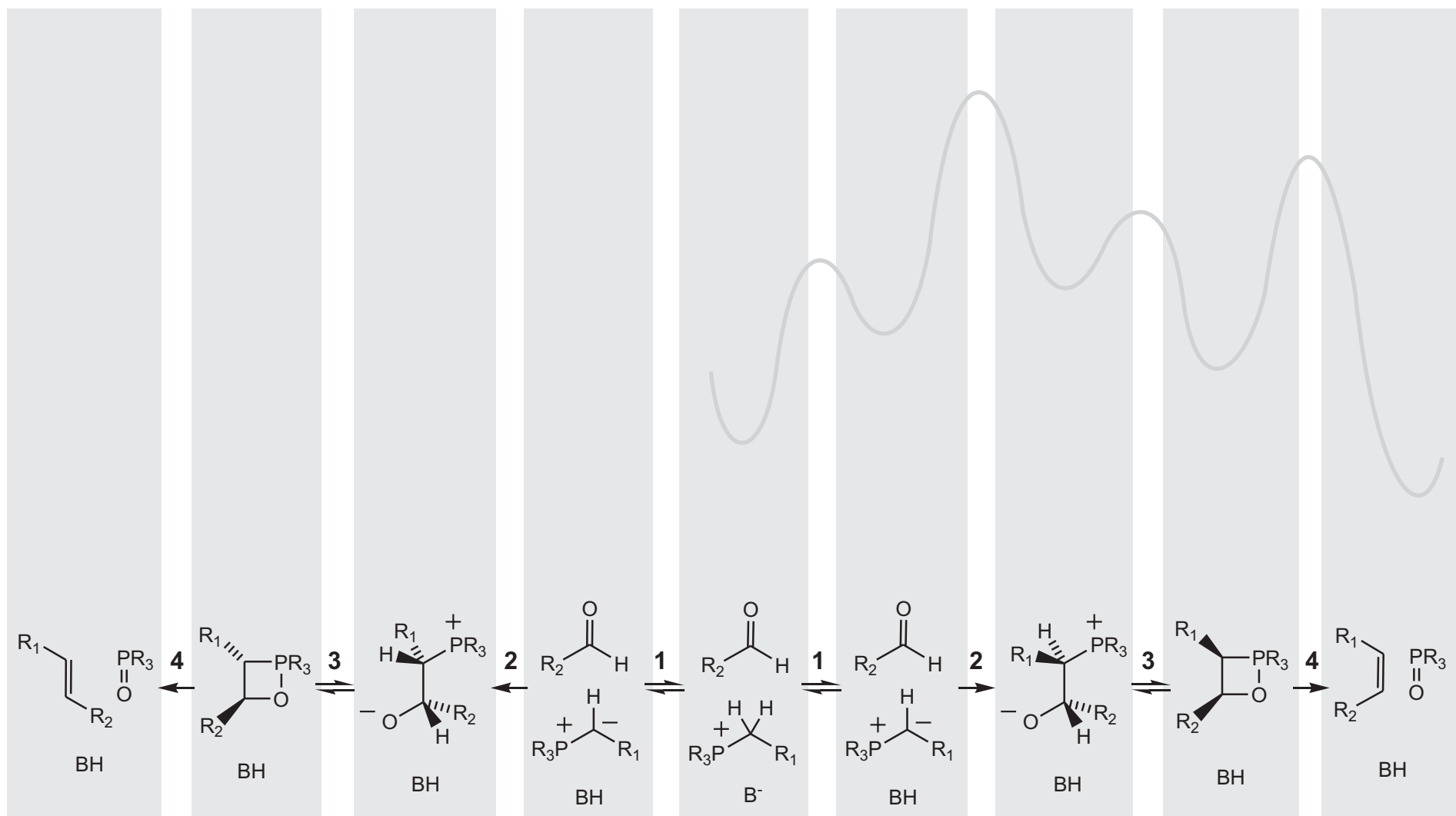
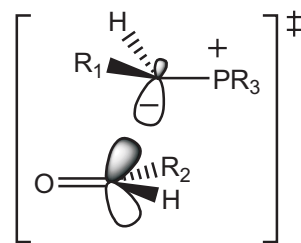
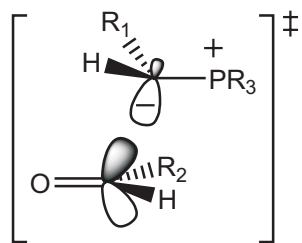
- c. When $-\text{PR}_3 = -\text{PO}(\text{OEt})_2$, on the other hand, the Wittig reaction² selectively yields *E*-(*trans*-)olefins—the thermodynamically more stable product. Presumably, step 2 is not rate-determining for this reaction variant because the phosphonate group is extremely electron-withdrawing, and stabilizes negative charge on the adjacent carbon. What effect would this substitution have on the energy levels you drew in part (b)? Re-draw these levels on the diagram on the next page; the gray curve is reproduced from the first diagram.
- d. It is important to note that *Z*- and *E*-olefins do not interconvert in the presence of diethylphosphonate:



What does this say about the possibility that the Wittig reaction is under “thermodynamic control” for $-\text{PR}_3 = -\text{PO}(\text{OEt})_2$? Complete your diagram on the next page to illustrate what determines the selectivity of the Wittig reaction for *E*-olefins for this substitution. In addition, draw any other relevant transition states or energetic interactions in intermediates or products (as I have for the transition state in step 2) to illustrate the preference here. Invoke the Curtin-Hammett Principle or Hammond Postulate wherever appropriate.

- e. What would you expect the relative magnitude and sign to be for ΔH^\ddagger and ΔS^\ddagger measured for each Wittig variant?

² Using phosphine oxide or phosphonate ester reactants in the Wittig reaction is sometimes called the *Horner-Wadsworth-Emmons modification*.



\leftarrow *to E-olefin* For $-\text{PR}_3 = -\text{PO}(\text{OEt})_2$ *to Z-olefin* \rightarrow