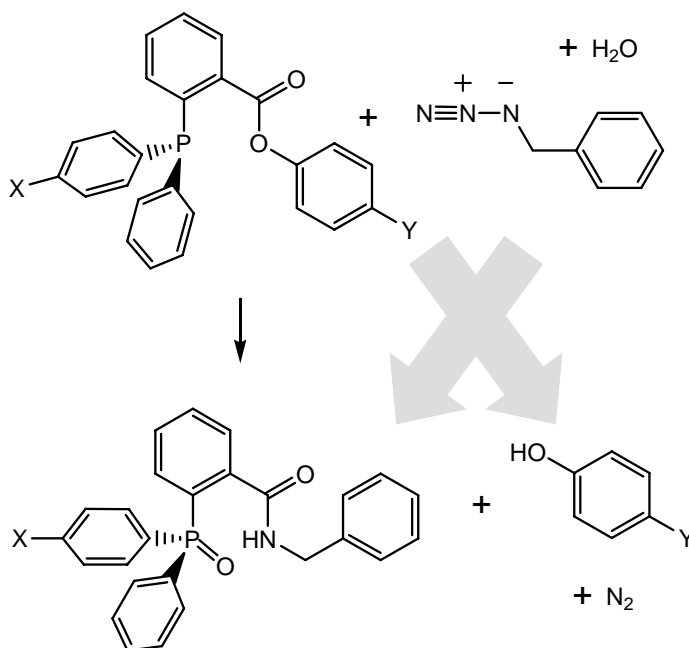


## Workshop 9

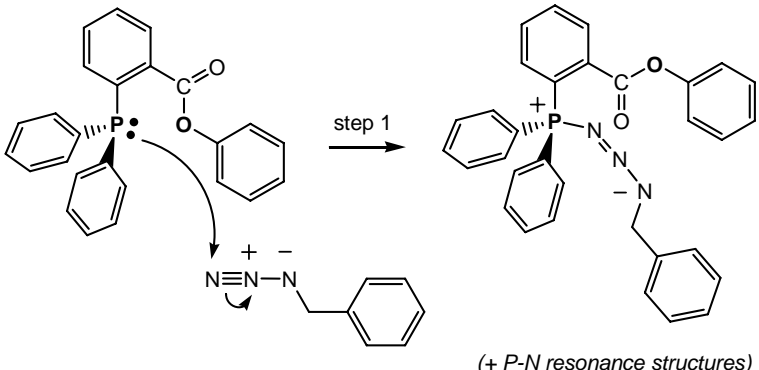
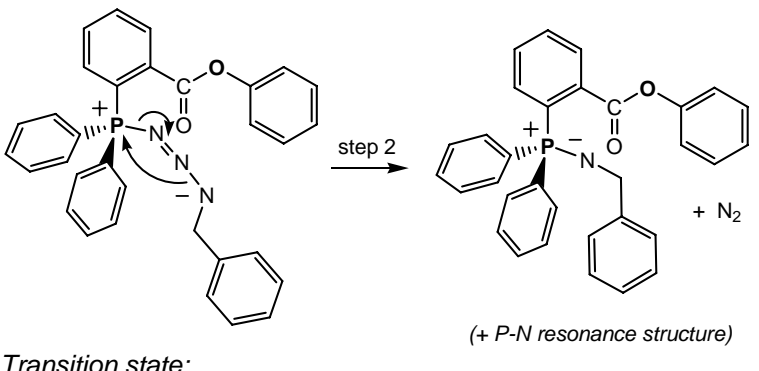
Carolyn Bertozzi (UC Berkeley) and coworkers have used the “Staudinger ligation” as a reaction for attaching synthetic molecules to specific proteins and sugars on the surfaces of living cells.<sup>1</sup> In parallel studies, the Bertozzi group has also examined the mechanism of the Staudinger ligation by performing kinetic measurements on starting materials with different substituents X and Y.<sup>2</sup> The goal of these studies was to construct linear free-energy relationships that could describe how charges at phosphorus and at the phenolic oxygen were affected in the rate-determining transition state.

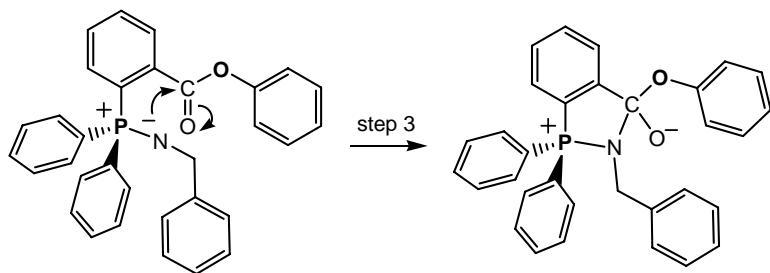


- A proposed mechanism for the Staudinger ligation is shown in tables on the next two pages. For each step in the mechanism, draw a transition state. Make sure that you label whole or partial charges, and illustrate which bonds are in the process of being made or broken. Keep in mind that resonance structures can contribute partial charge to a structure, and that neutral phosphorus can be either tri- or pentavalent.
- In the same table, write whether positive or negative charge density increases, decreases, or doesn't change at phosphorus and at phenolic oxygen (shown in bold) relative to starting material.
- Again on the same chart, use your answer for part (a) to describe what the effect of electron-withdrawing substituents at positions X and Y would have on the overall rate of reaction (and rate constant  $k$ ), relative to X = H and Y = H.
- Hammett plots that relate rate constants for different substituents X and Y to the parameter  $\sigma^+$  are shown on page 4. What values  $\rho_X$  and  $\rho_Y$  do you estimate from these plots? What do these values mean?
- Based on all of this information, which of the steps in the mechanism might be rate-determining, and which cannot be?

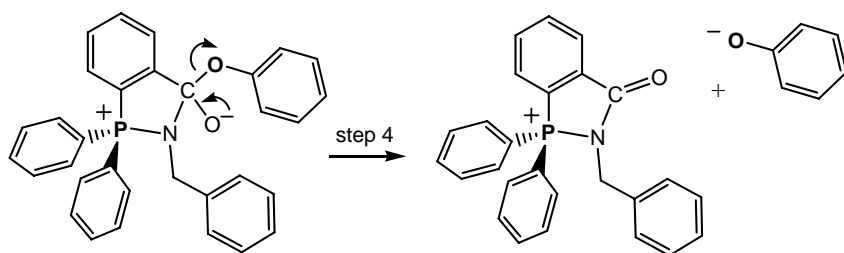
<sup>1</sup> Saxon, E.; Bertozzi, C. R. *Science* **2000**, 287, 2007-2010.

<sup>2</sup> Lin, F. L.; Hoyt, H. M.; van Halbeek, H.; Bergman, R. G.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2005**, 127, 2686-2695.

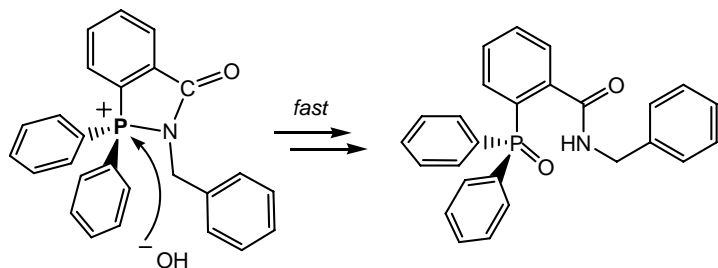
 <p><i>Transition state:</i></p>	<p>TS more/less +/- than SM at P?</p>	<p>TS more/less +/- than SM at O?</p>
	<p>Effect of EWG X on <math>k</math>?</p>	<p>Effect of EWG Y on <math>k</math>?</p>
 <p><i>Transition state:</i></p>	<p>TS more/less +/- than SM at P?</p>	<p>TS more/less +/- than SM at O?</p>
	<p>Effect of EWG X on <math>k</math>?</p>	<p>Effect of EWG Y on <math>k</math>?</p>



Transition state:

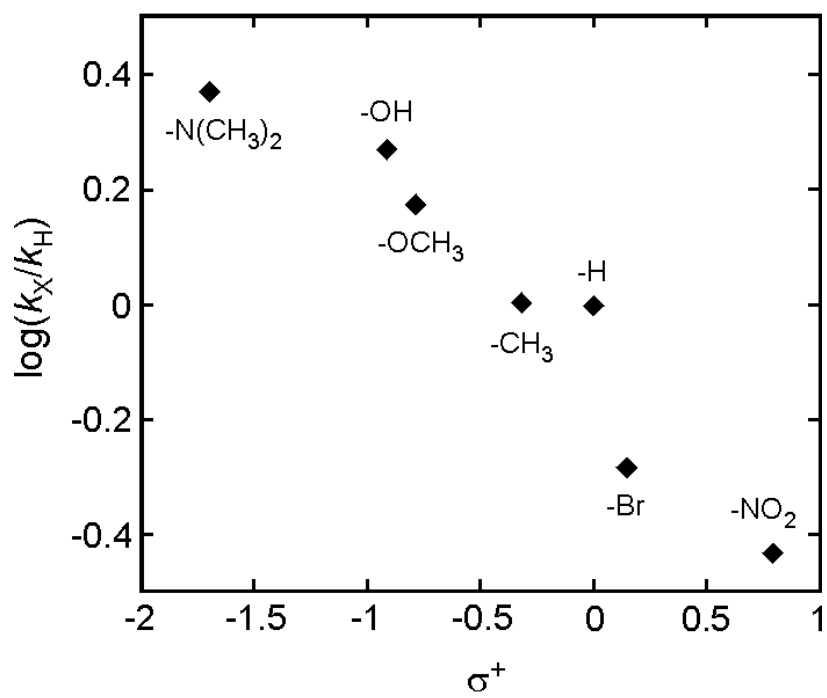


Transition state:

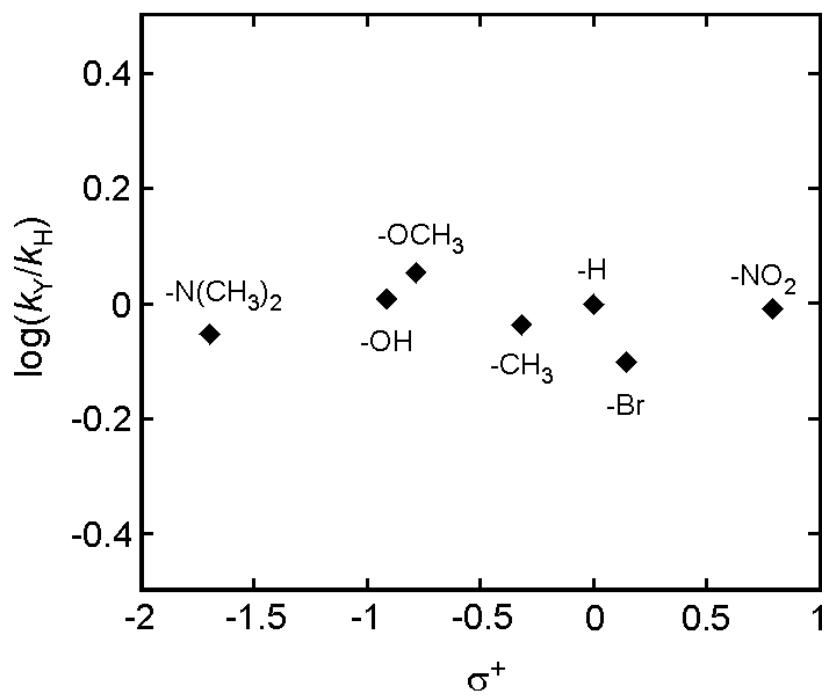


TS more/less +/- than SM at <b>P</b> ?	TS more/less +/- than SM at <b>O</b> ?
Effect of EWG <b>X</b> on <i>k</i> ?	Effect of EWG <b>Y</b> on <i>k</i> ?
TS more/less +/- than SM at <b>P</b> ?	TS more/less +/- than SM at <b>O</b> ?
Effect of EWG <b>X</b> on <i>k</i> ?	Effect of EWG <b>Y</b> on <i>k</i> ?

*substituents X*



*substituents Y*



*Substituent effect problems to try on your own:*

MPOC, Chapter 8: Problems 11, 12, 14, 18.