

# LS 2022

Lecture 4: 2022-12-15

# Determining Reaction Mechanisms



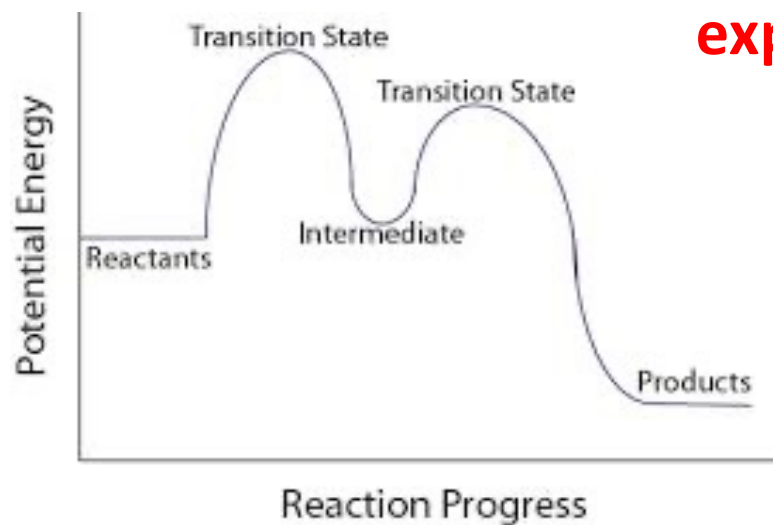
**Hammett plot**



**Crossover  
experiment**

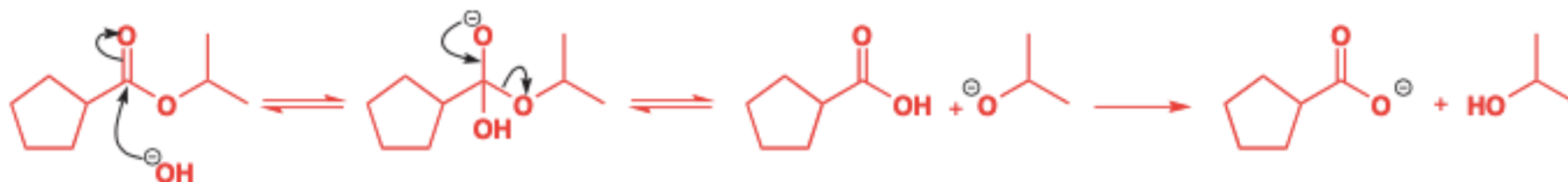
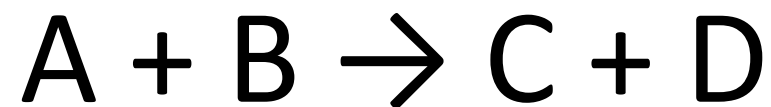


**Labelling  
experiment**

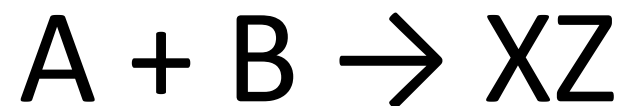


**KIE  
Kinetic isotope  
experiment**

# Reaction mechanism







What we do when C and D are not obtained?



# Reaction mechanism

## General guideline to find out an explanation

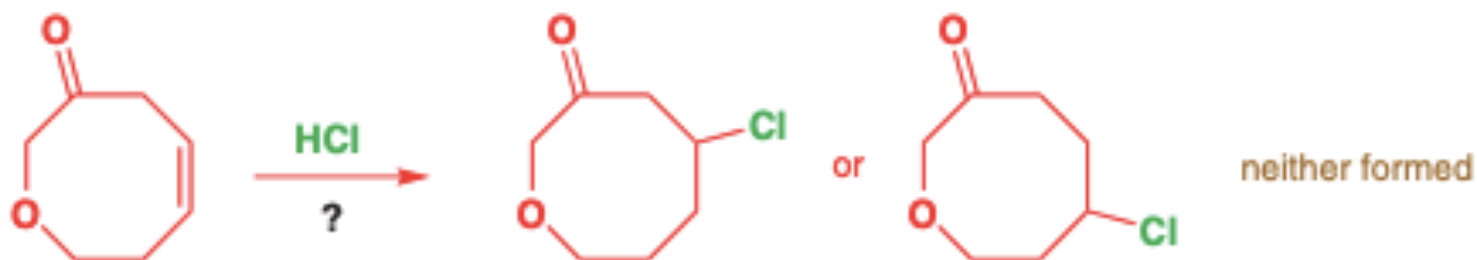
-  Structure identification (determining exactly what the product is).
-  Determining the number of steps, and the structure of intermediates.
-  Finding out the slow (rate determining) step.
-  Finding any catalysis.

# Reaction mechanism

## Be sure of the structure of the product

Not always an obvious point

Addition of HCl to this alkene

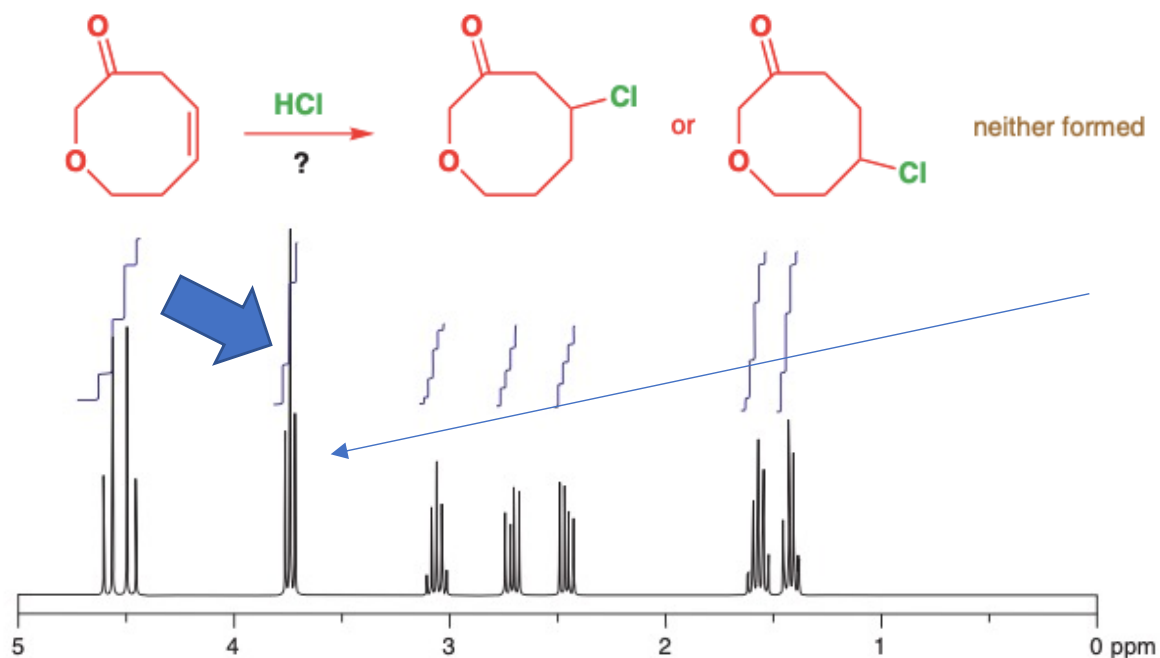


Expected mechanism

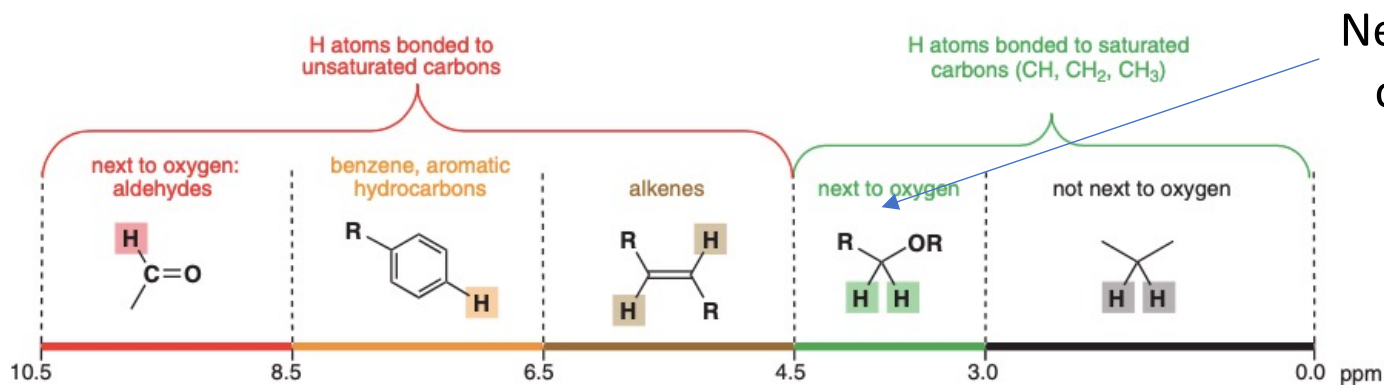


# Reaction mechanism

- Find out for sure what the structure of the product is before you start a mechanistic investigation.



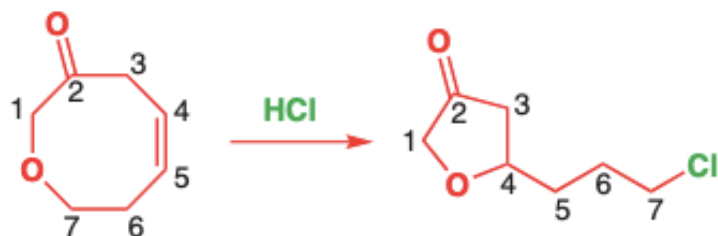
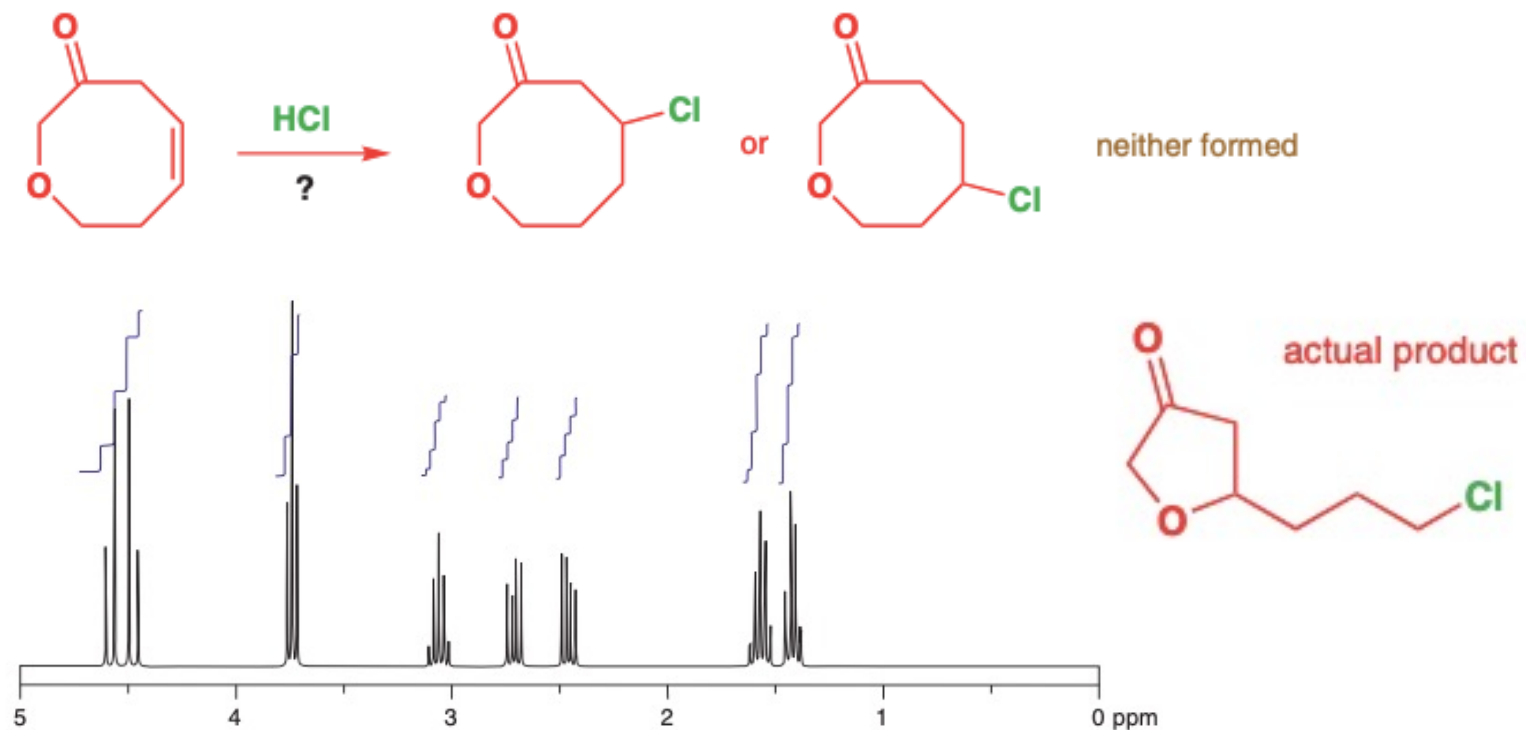
Simple signal suggest a linear X-CH<sub>2</sub>-R. No longer an 8-membered ring.



Next to oxygen or halogens.

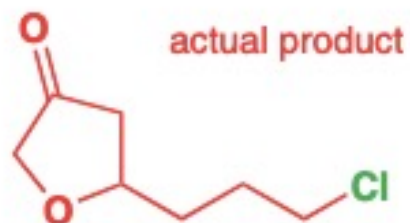
# Reaction mechanism

- Find out for sure what the structure of the product is before you start a mechanistic investigation.



# Reaction mechanism

- Find out for sure what the structure of the product is before you start a mechanistic investigation.



It's a well-known transannular reaction.

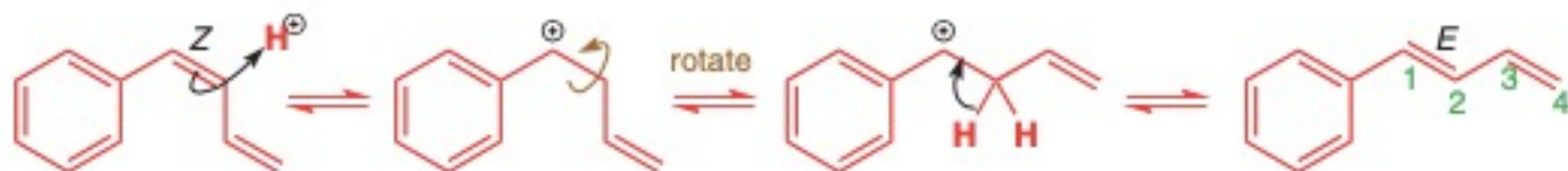


Don't spend long time to investigate a "reported transformation".



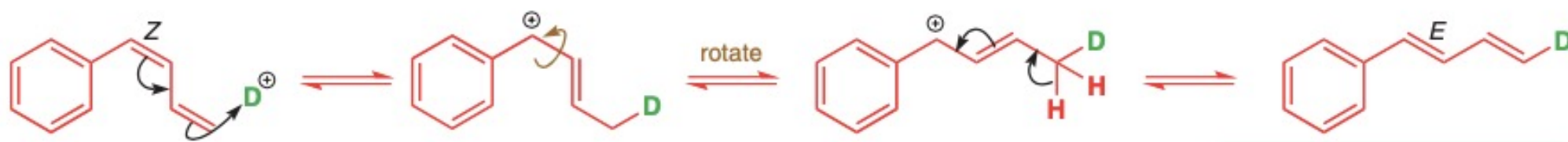
# Reaction mechanism

## Labelling experiments reveal the fate of individual atoms



The isomerization of Z-1-phenylbutadiene to the E diene in acid looks like a simple reaction. Protonation of the Z alkene would give a stabilized secondary benzylic cation that should last long enough to rotate. Loss of the proton would then give the more stable E diene.

## Experiment conducted with $D^+$ of $D_2O$



# Reaction mechanism

- **Top tip for rearrangements**

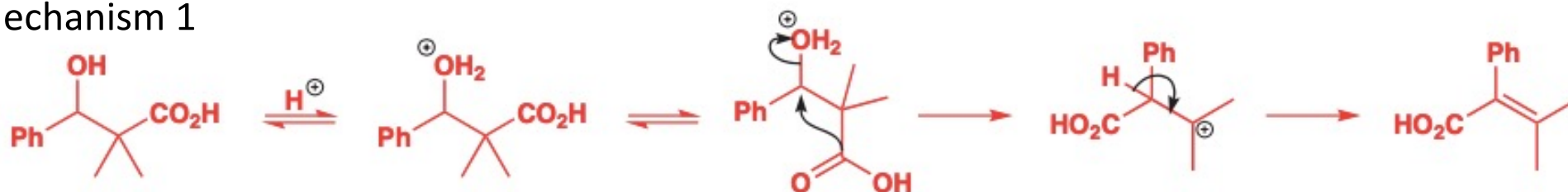
Number the carbon atoms in the starting material and product before you try to work out the mechanism.



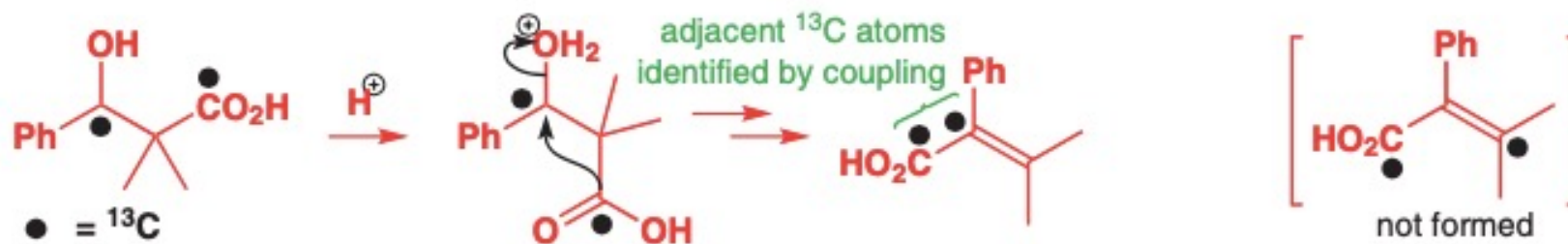
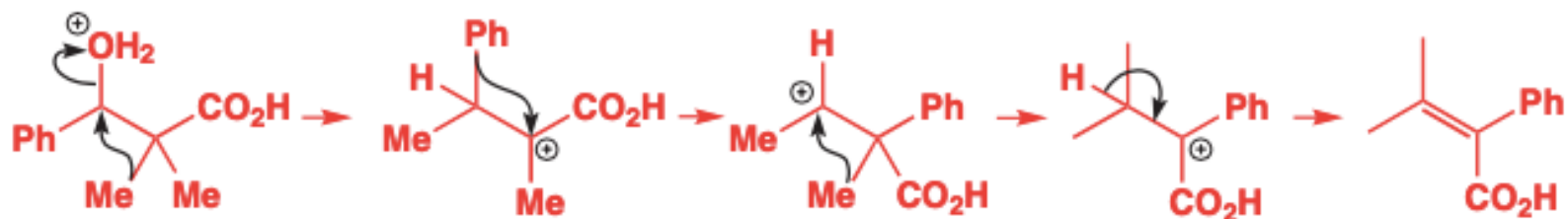
# Reaction mechanism

## Double labelling experiments

Mechanism 1

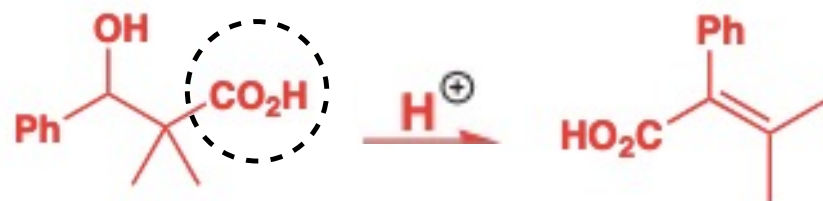


Mechanism 2

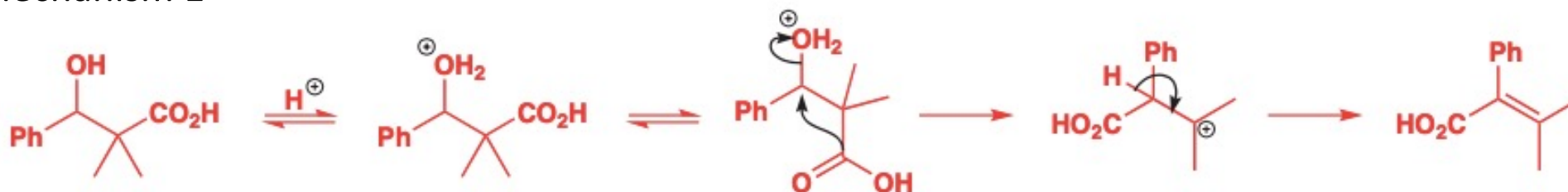


# Reaction mechanism

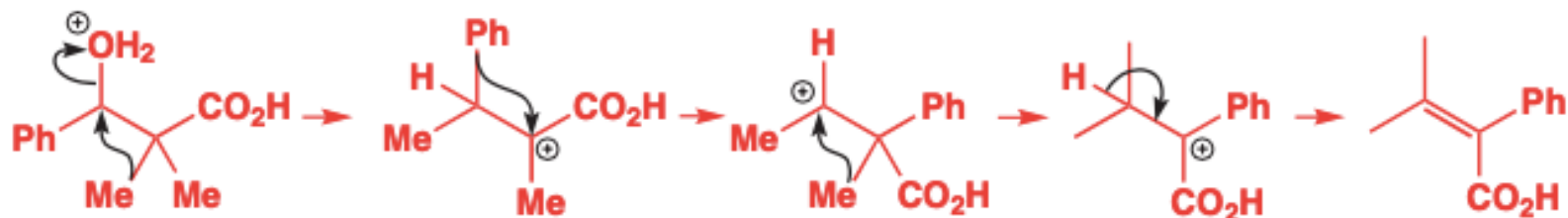
## Double labelling experiments



Mechanism 1

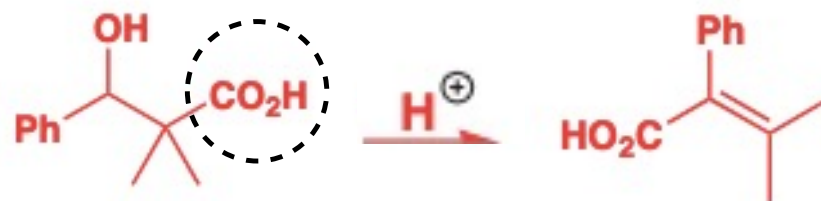


Mechanism 2

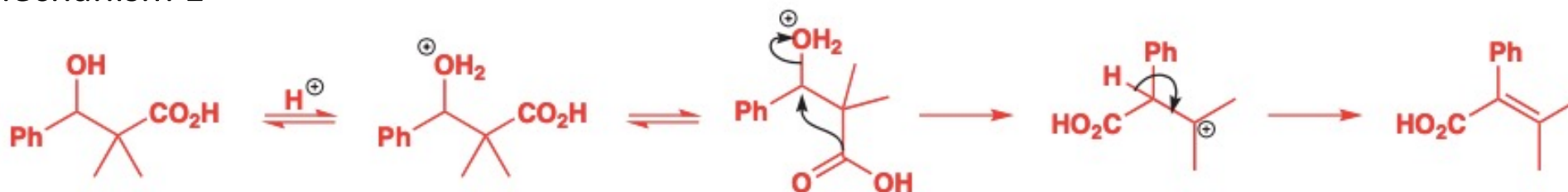


# Reaction mechanism

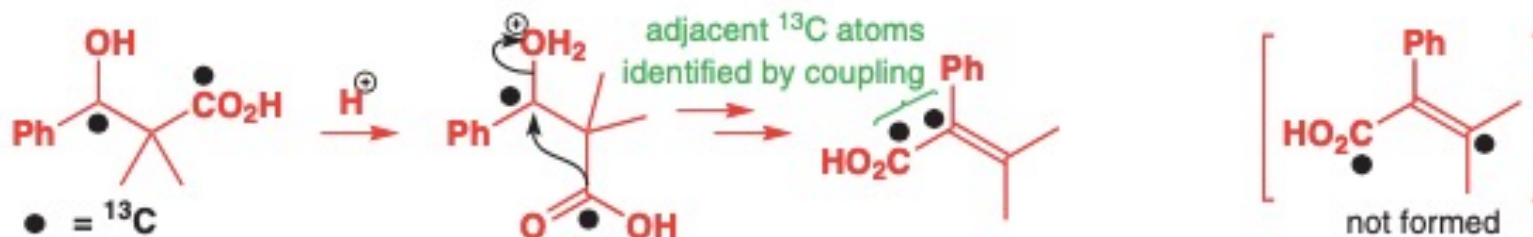
## Double labelling experiments



### Mechanism 1



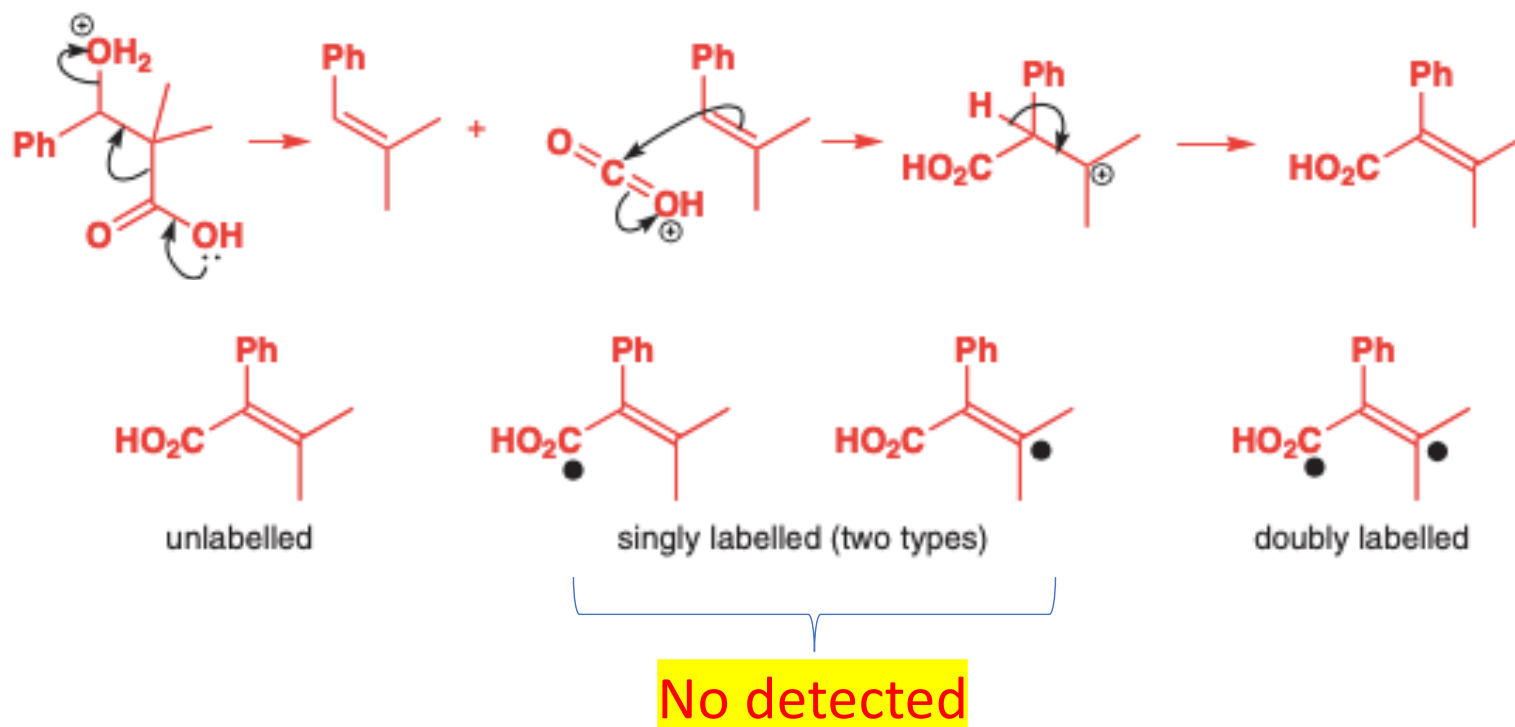
■ We don't normally see <sup>13</sup>C-<sup>13</sup>C coupling because in most molecules only 1.1% of the C atoms are <sup>13</sup>C, so there's little chance of two of them finding themselves adjacent to one another. But when both C atoms are always <sup>13</sup>C, the coupling becomes evident.



# Reaction mechanism

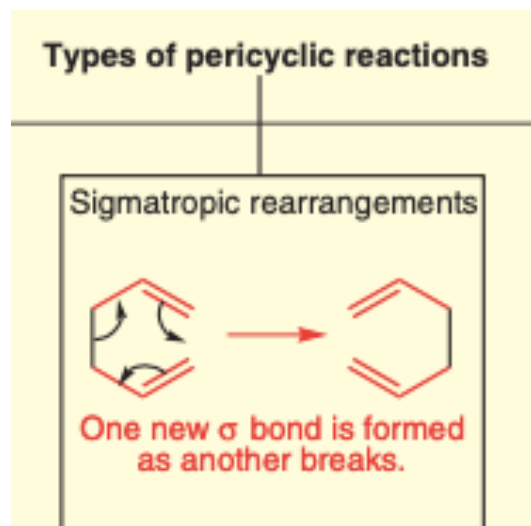
## 'Crossover' experiments

### Mechanism 3

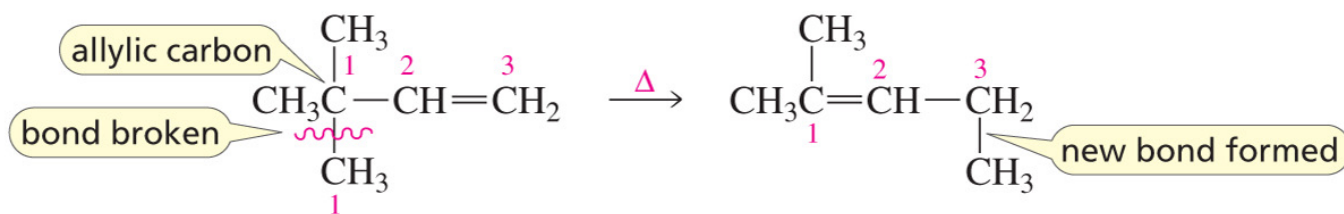


This mechanism can be checked by using a 50:50 mixture of doubly labelled and unlabelled starting material. The molecule of alkene that captures the roving protonated labelled CO<sub>2</sub> might happen to be labelled too but equally well it might be unlabelled. If this last mechanism is correct, we should get a mixture of unlabelled, singly labelled, and doubly labelled product in the ratio 1:2:1 as there are two types of singly labelled product.

# Reaction mechanism



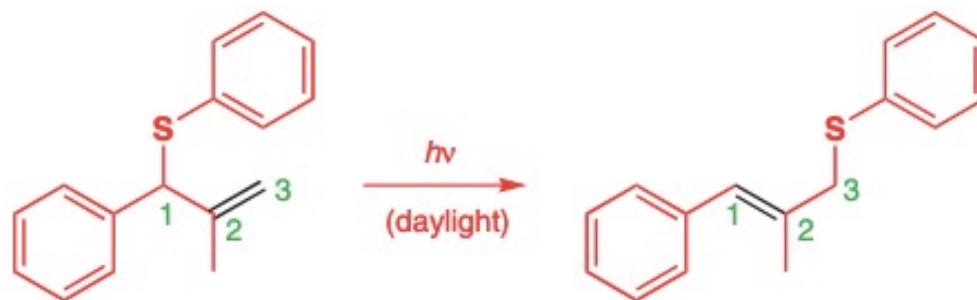
## [1,3] sigmatropic rearrangement



# Reaction mechanism

## Crossover experiments

Crossover experiments demand some sort of double labelling, which does not have to be isotopic. An example where crossover products are observed is the light-initiated isomerization of allylic sulfides.

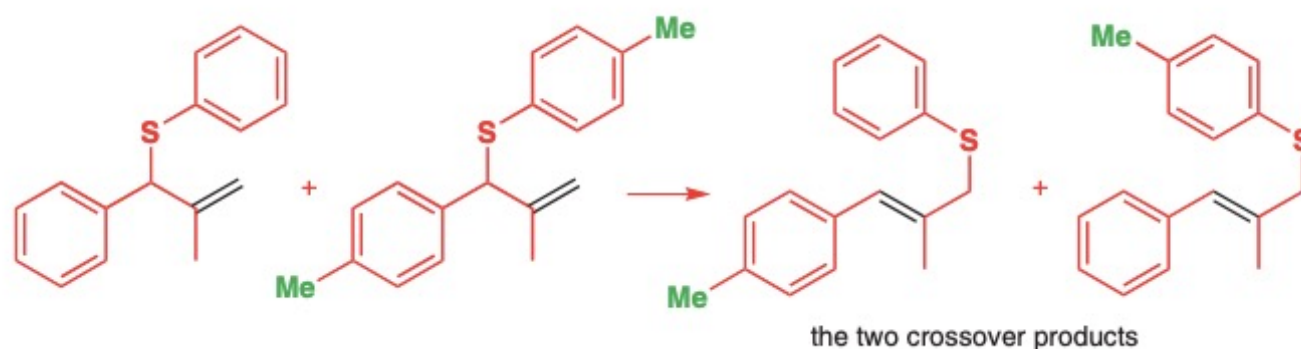


It looks like a general 1,3-sigmatropic rearrangement, but....



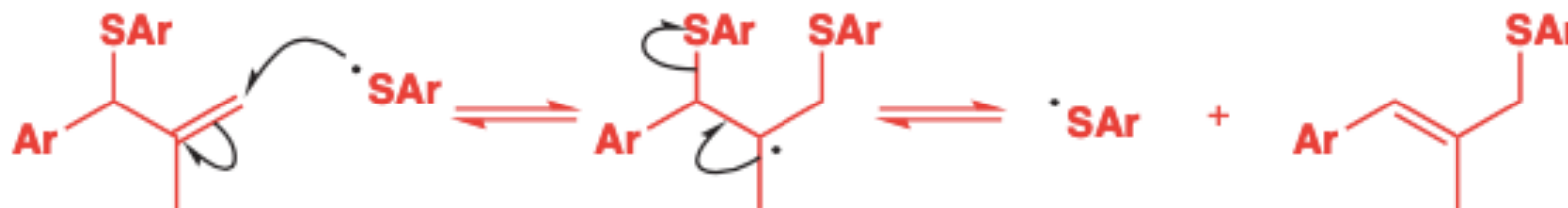
# Reaction mechanism

## Crossover experiments

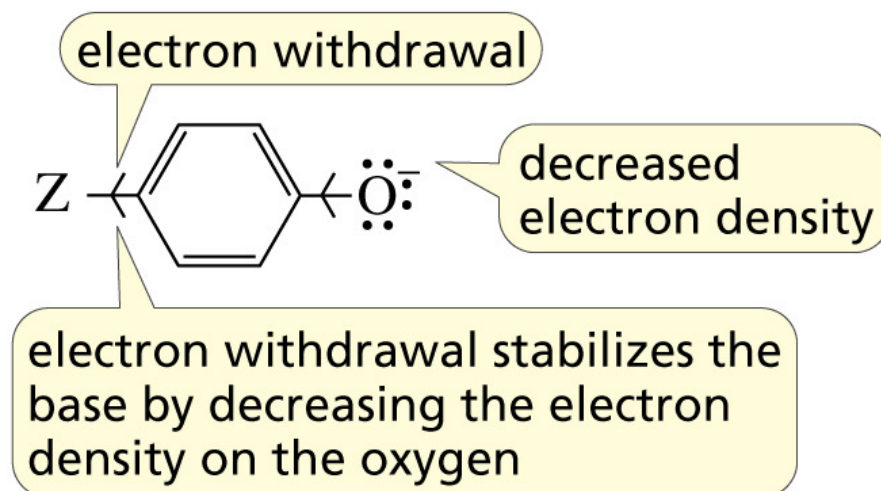
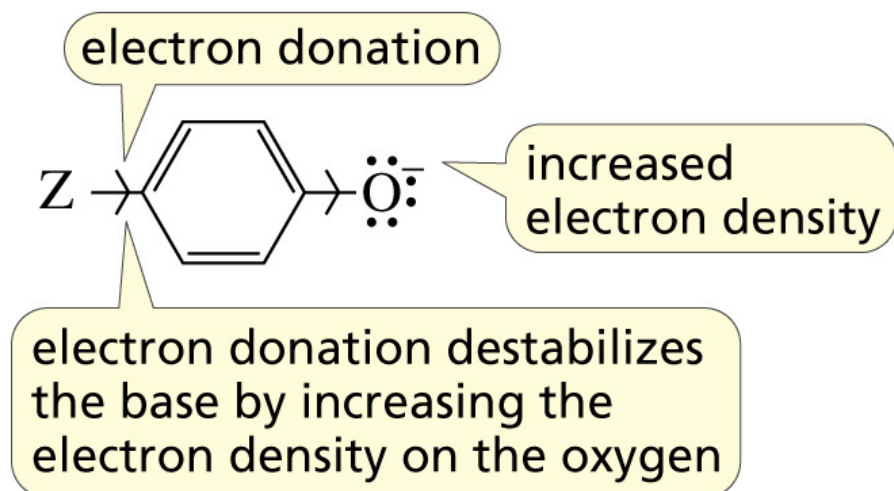


Products having 2 phenyl and 2 para-tolyl.

The results suggest that intramolecular rearrangement is unlikely.



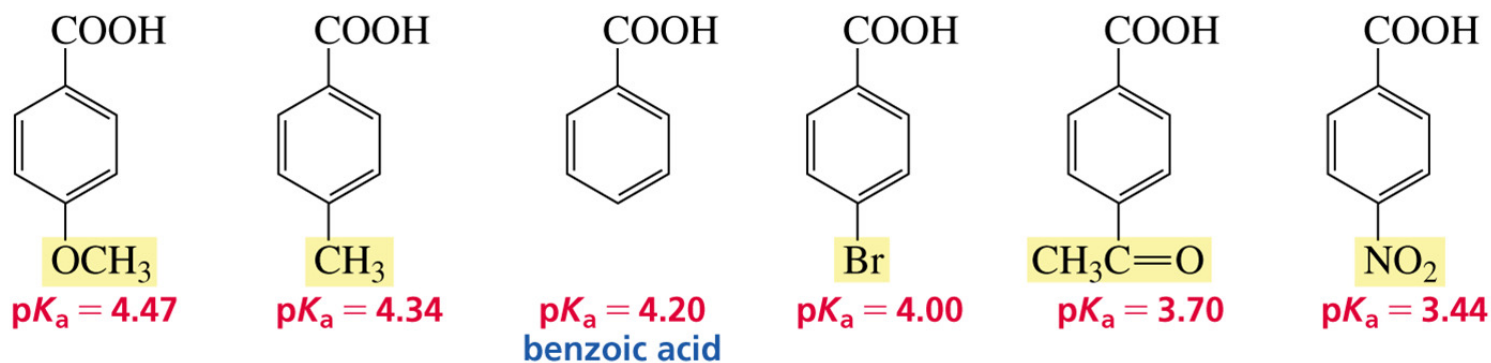
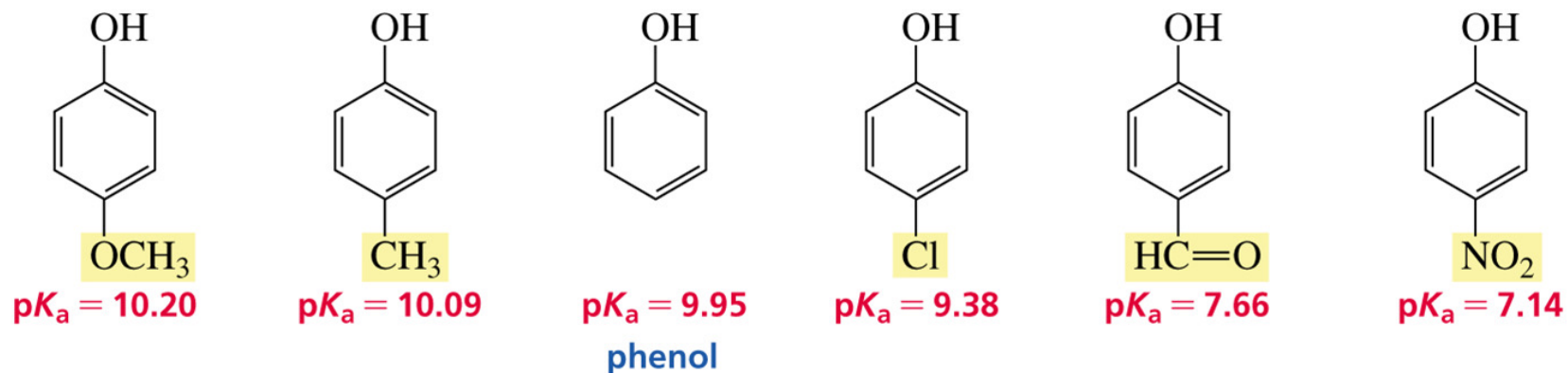
# Electronic Effects



Electron donation **decreases** acidity.

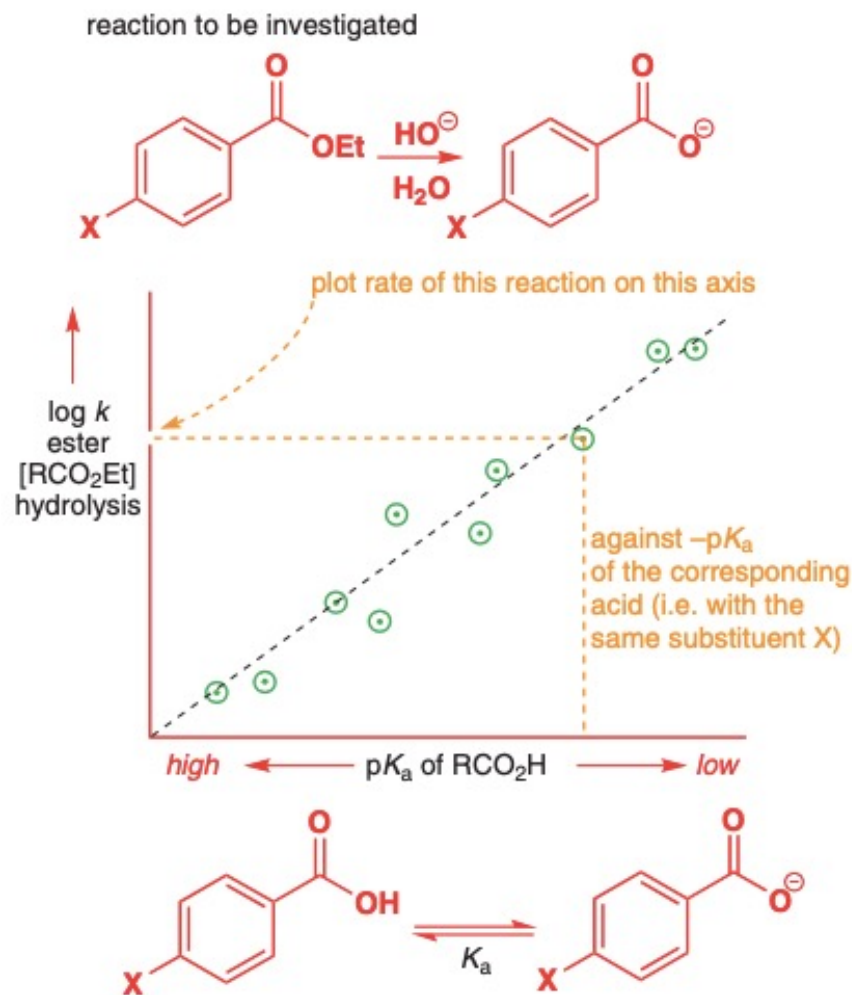
Electron withdrawal **increases** acidity.

# Electronic Effects and $pK_a$ Values



# Reaction mechanism

## Hammett relationship




Quantify the effects of EDG and EWG on the transition state or intermediate during a reaction.

Different groups at para position were studied. Meta and ortho-substituents are not considered to eliminate the steric effect.

# Reaction mechanism

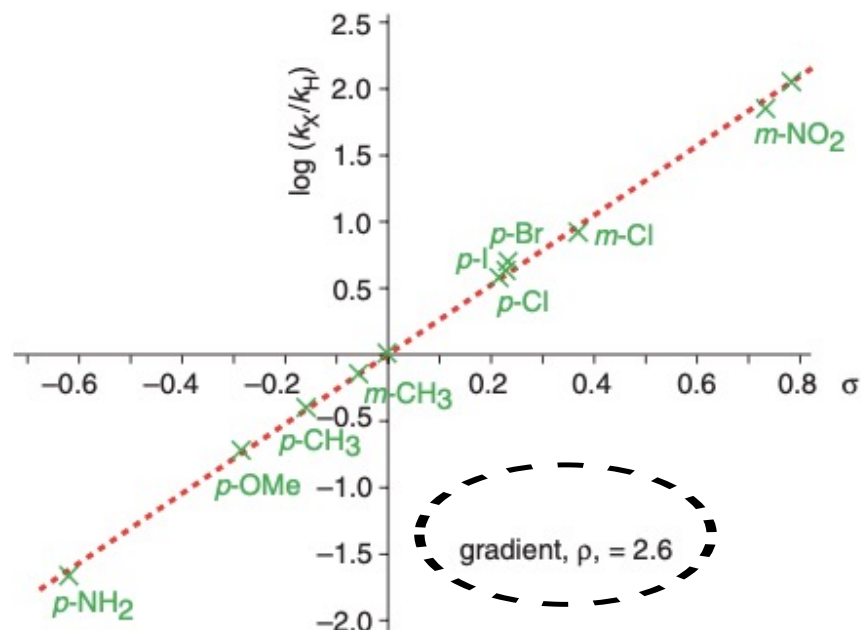
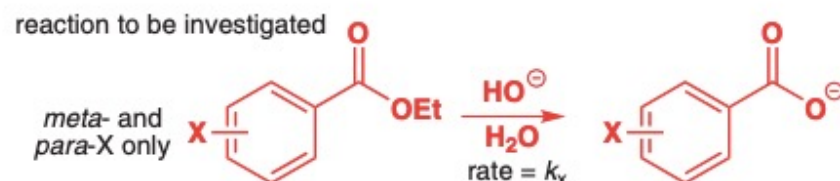
## The Hammett substituent constant $\sigma$

$$\sigma_x = \log\left(\frac{K_a(\text{XC}_6\text{H}_4\text{COOH})}{K_a(\text{C}_6\text{H}_5\text{COOH})}\right) = \text{p}K_a(\text{C}_6\text{H}_5\text{COOH}) - \text{p}K_a(\text{XC}_6\text{H}_4\text{COOH})$$

Substituent X	pK <sub>a</sub> of <i>p</i> -XC <sub>6</sub> H <sub>4</sub> COOH	pK <sub>a</sub> of <i>m</i> -XC <sub>6</sub> H <sub>4</sub> COOH	$\sigma_p$	$\sigma_m$	Comments
NH <sub>2</sub>	4.82	4.20	-0.62	0.00	groups that donate electrons have negative $\sigma$
OCH <sub>3</sub>	4.49	4.09	-0.29	0.11	
CH <sub>3</sub>	4.37	4.26	-0.17	-0.06	
 H	4.20	4.20	0.00	0.00	there are no values for <i>ortho</i> substituents
F	4.15	3.86	0.05	0.34	
I	3.97	3.85	0.23	0.35	
Cl	3.98	3.83	0.22	0.37	$\sigma_p < \sigma_m$ for inductive withdrawal
Br	3.97	3.80	0.23	0.40	
CO <sub>2</sub> CH <sub>3</sub>	3.75	3.87	0.45	0.33	
COCH <sub>3</sub>	3.71	3.83	0.49	0.37	$\sigma_p > \sigma_m$ for conjugating substituents
CN	3.53	3.58	0.67	0.62	
NO <sub>2</sub>	3.43	3.47	0.77	0.73	groups that withdraw electrons have positive $\sigma$

# Reaction mechanism

## The Hammett reaction constant $\rho$



$k_x$  = rate constant of the reaction with the substituted benzoate  
 $k_H$  = rate constant of the reaction for the unsubstituted benzoate H

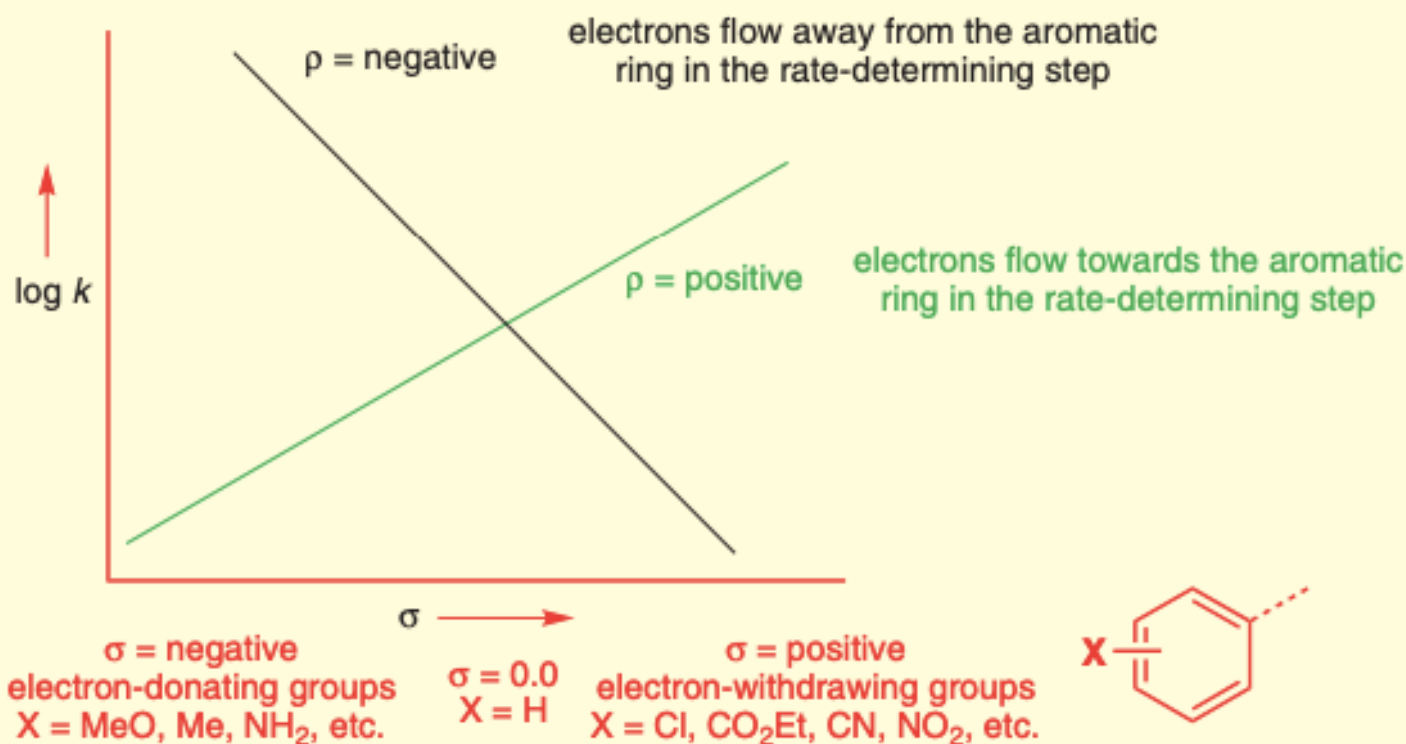
The gradient of this best-fit line, given the symbol  $\rho$  (rho), tells us how sensitive the reaction is to substituent effects in comparison with the ionization of benzoic acids. The gradient is  $\rho = +2.6$ . This tells us that the reaction responds to substituent effects in the same way (because it is +) as the ionization of benzoic acids but by much more ( $10^{1.6}$  times more) because it is 2.6 instead of 1.0.

# Reaction mechanism

● The Hammett reaction constant  $\rho$  measures the *sensitivity* of the reaction to electronic effects.

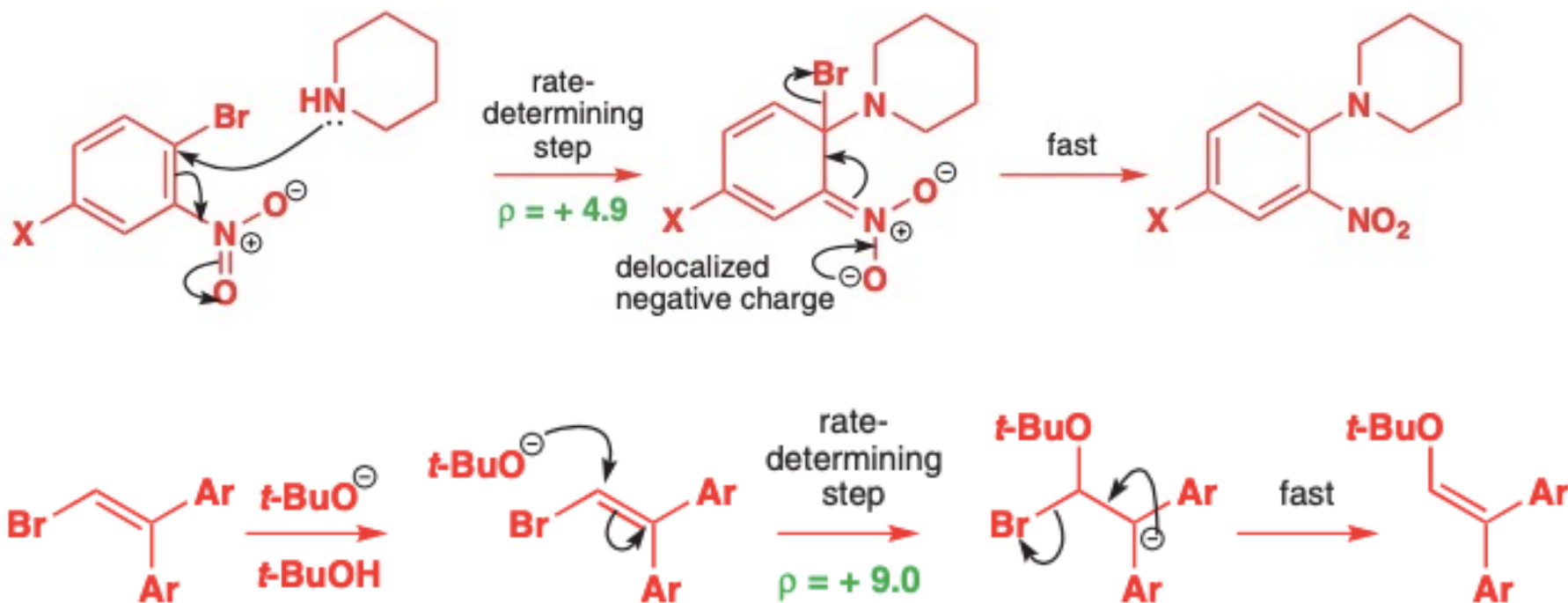
- A *positive*  $\rho$  value means *more* electrons in the transition state than in the starting material.
- A *negative*  $\rho$  value means *fewer* electrons in the transition state than in the starting material.

typical Hammett plots



# Reaction mechanism

## Reactions with positive Hammett $\rho$

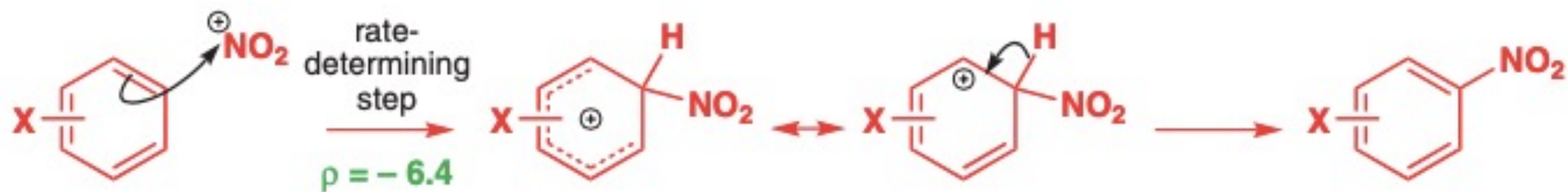
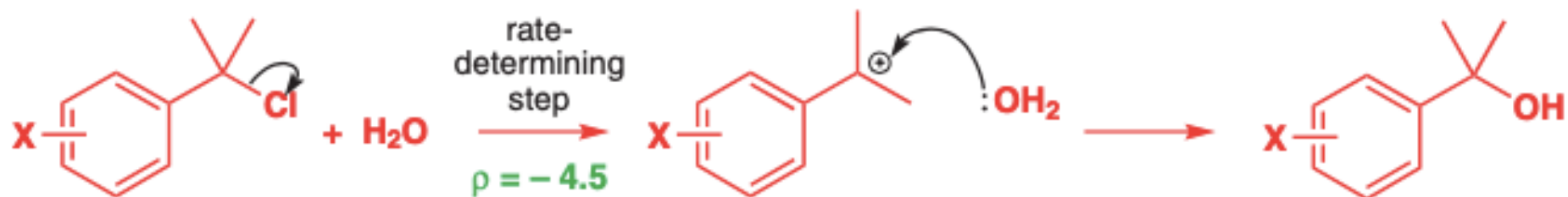


The size and sign of the value of  $\rho$  tell us about what is happening *in the rate-determining step* of a reaction.



# Reaction mechanism

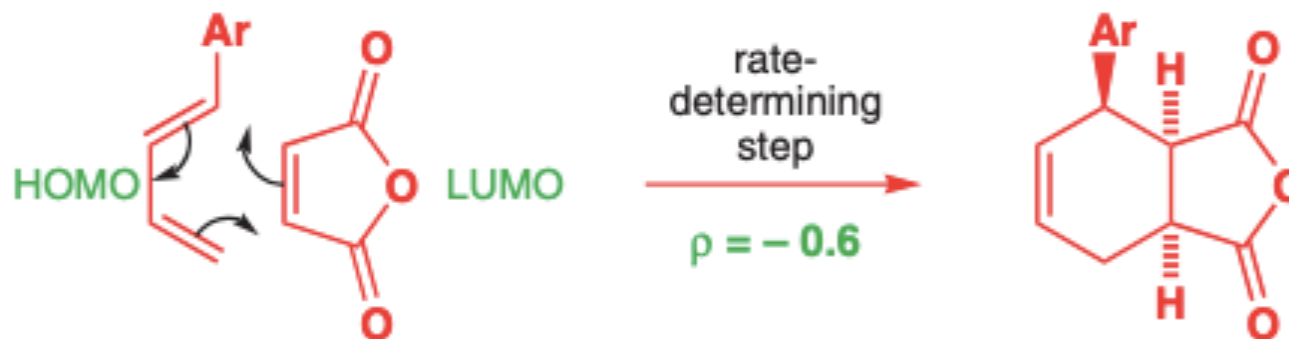
## Reactions with negative Hammett $\rho$



Negative  $\rho$  values mean electrons flowing out of the ring.

# Reaction mechanism

## Reactions with small Hammett $\rho$

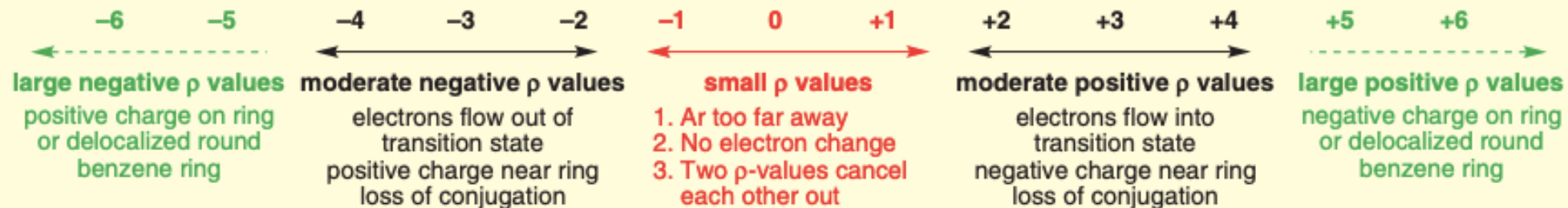


A case is when the reaction is not dependent on electrons flowing into or out of the ring. A small effect on the HOMO orbital.

# Reaction mechanism

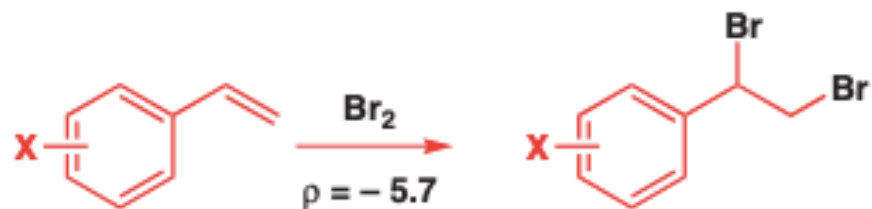
## Summary

### ● Summary: interpreting Hammett $\rho$ values



# Reaction mechanism

## Using the Hammett $\rho$ values to uncover mechanisms



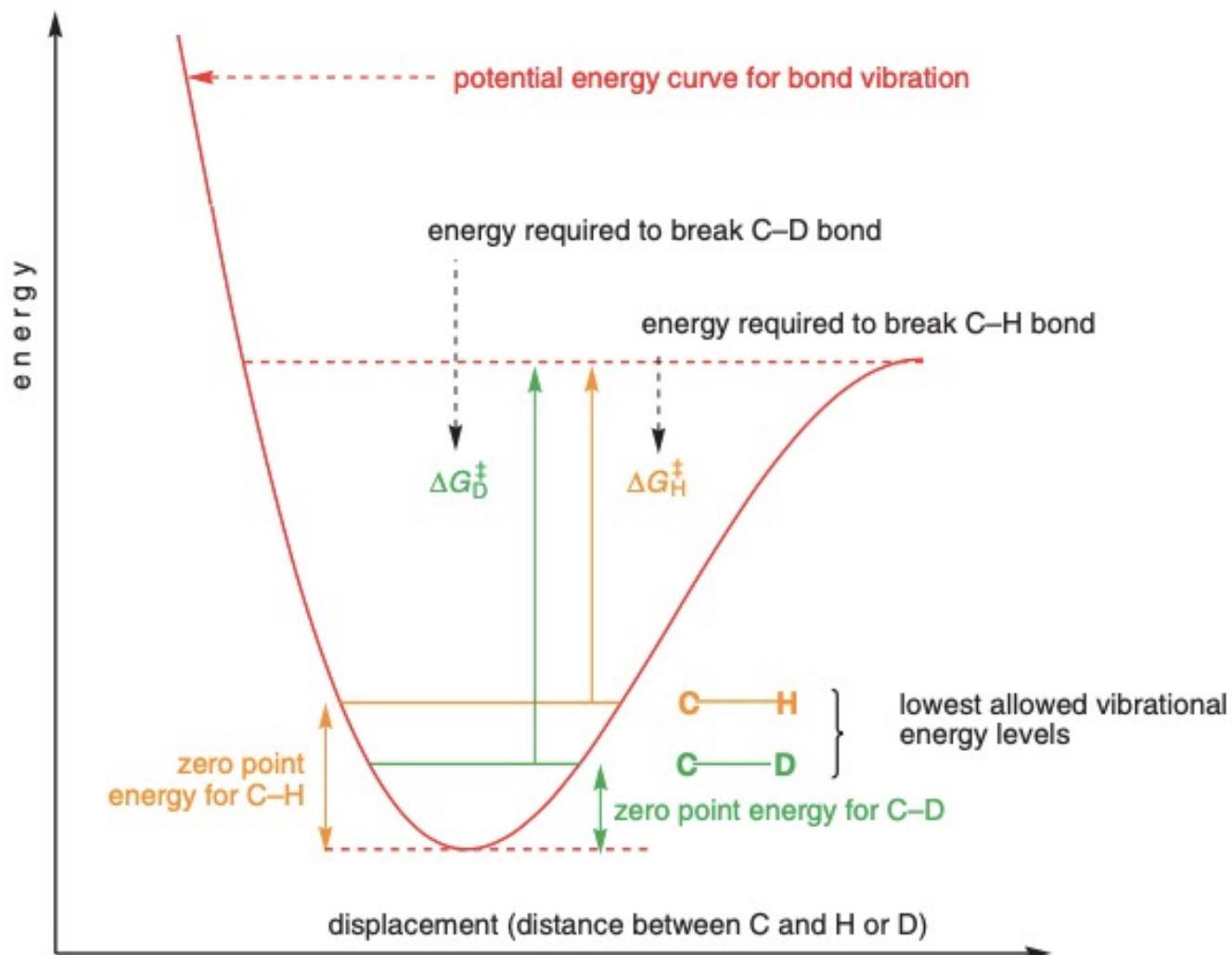
# Reaction mechanism

## Kinetic isotope effect KIE

Relies on the difference of atomic mass.

$$\text{KIE} = k_{\text{H}}/k_{\text{D}}$$

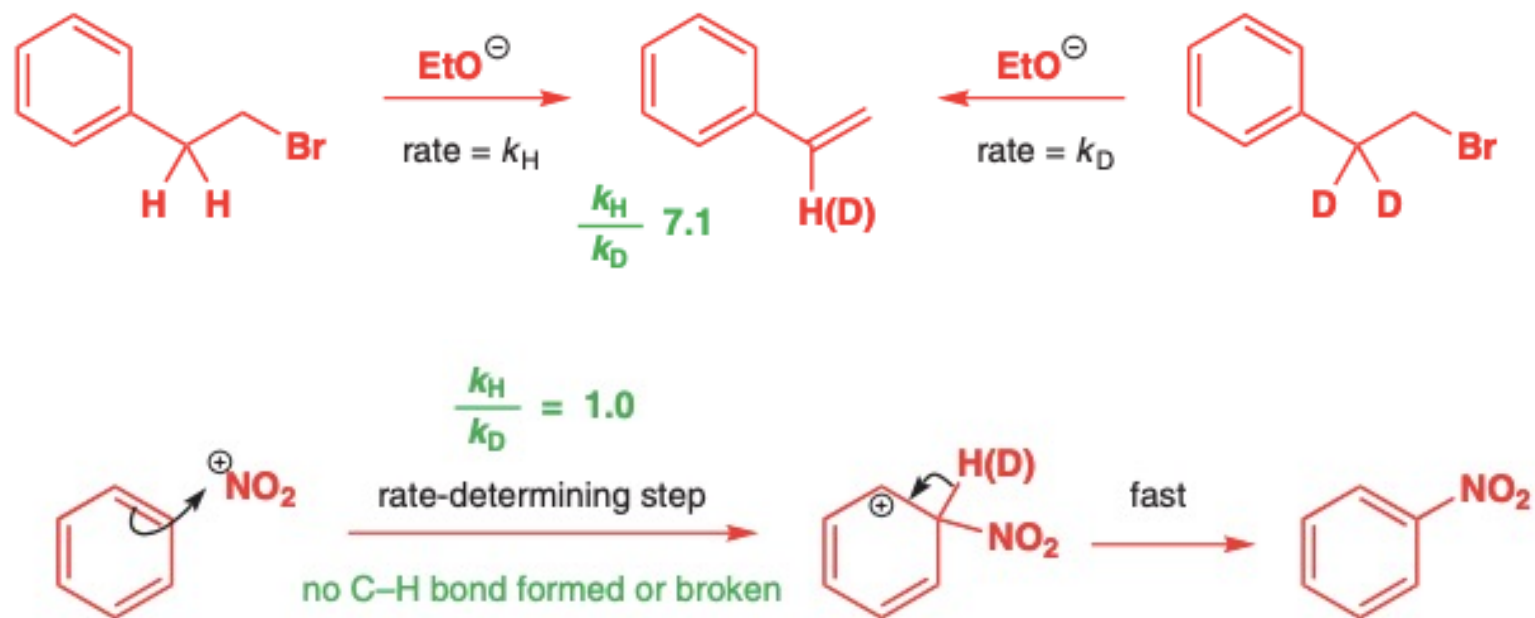
zero point energy and kinetic isotope effects



# Reaction mechanism

## Kinetic isotope effect KIE

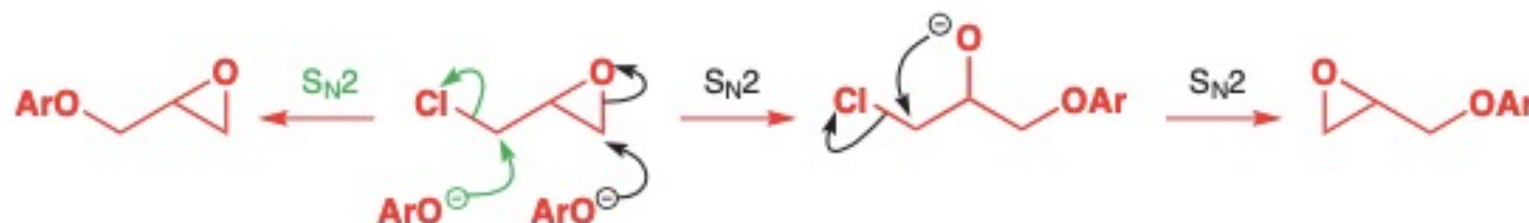
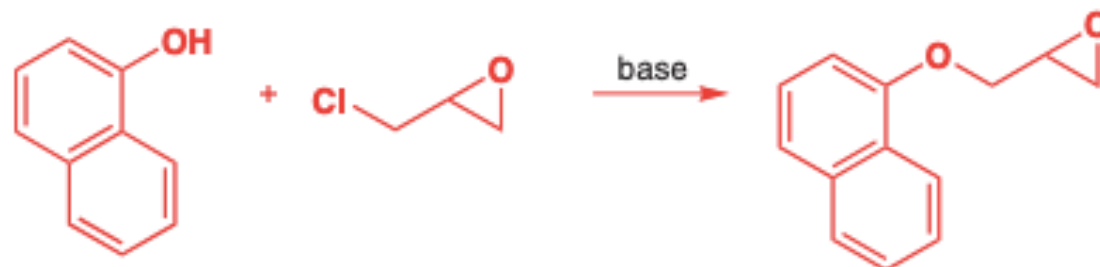
$$\text{KIE} = k_{\text{H}}/k_{\text{D}}$$



# Reaction mechanism

## Stereochemistry and mechanism

Retention or inversion?



# Reaction mechanism

