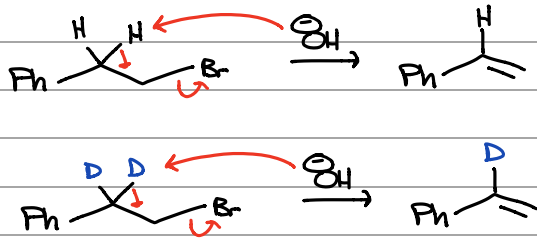
Kinetic Isotope Effects

- Isotopes have the same chemical properties. Labeling will not change the mechanism.



- Isotopes can minimally perturb the rxn leading to a change in rxn rate.

$KIE = \frac{k_H}{k_D}$ ← light isotope / ← heavy isotope

For the above elimination $\frac{k_H}{k_D} = 7$

Origin:

Vibrational states are quantized

The lowest energy vibrational state = zero point energy (ZPE)

$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{m_r}}$ ← force constant / ← reduced mass

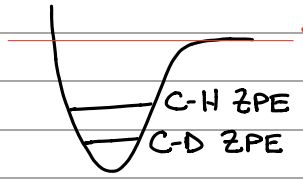
$m_r = \frac{m_x \cdot m_{molecule}}{m_x + m_{molecule}}$

	X = H	X = D
	$\frac{1 \cdot 184}{1+184}$	$\frac{2 \cdot 186}{2+186}$
	= 0.995	= 1.99

ν_H = Larger / Higher E vibration

ν_D = Smaller / Lower E vibration ⇐ Lower ZPE

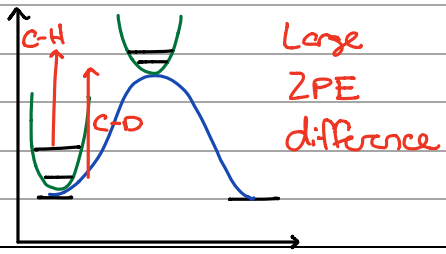
Morse Potential

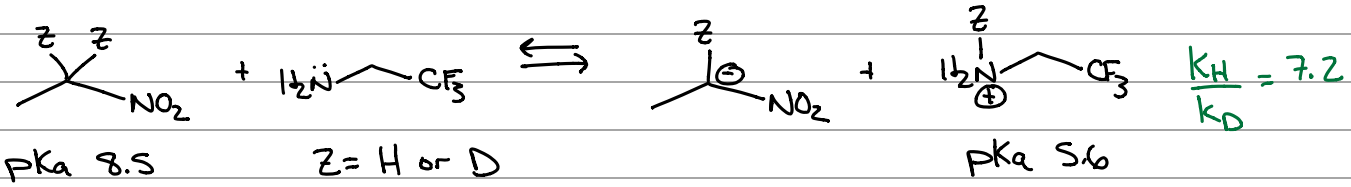


Breaking C-H requires less energy than C-D

If C-H/D bond is breaking in the RDS, k_H should be > than k_D

KIE is largest for thermoneutral reactions w/ a linear transition state





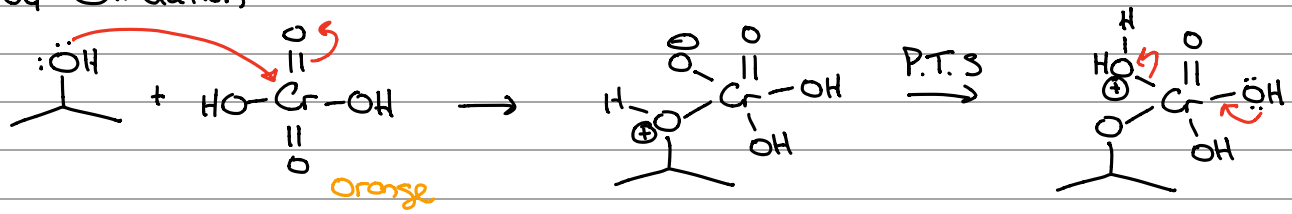
This is a **primary kinetic isotope effect**

↳ C-H / C-D bond breaks in the RDS

Maximum of ~8

Lower for early or late transition states

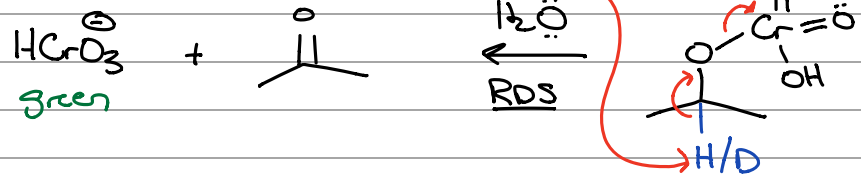
H_2CrO_4 Oxidation



With C-D, the color change is much slower

Primary KIE

$k_H/k_D = 5.9$

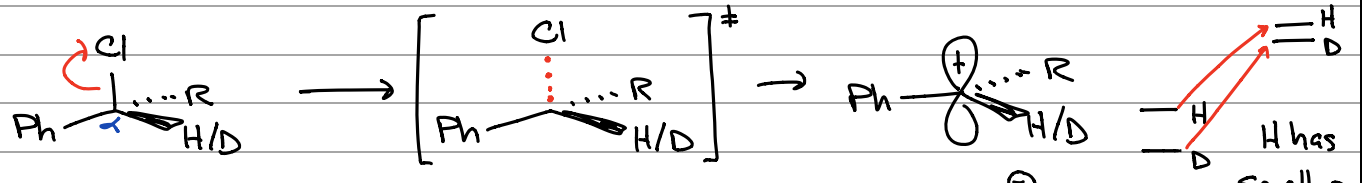


NMR, GL, HPLC can all be used to determine product ratios to measure KIE.

Secondary Kinetic Isotope Effect

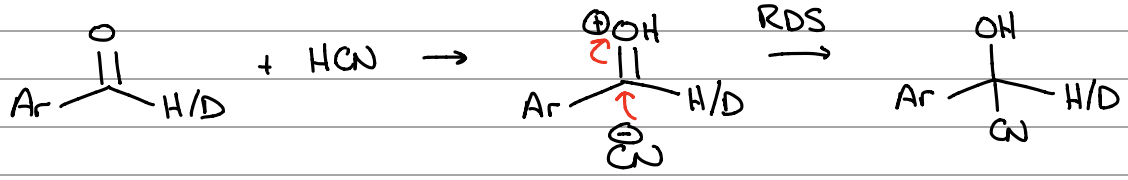
- C-H / C-D bonds are close to the reactive site, but do not break in the RDS.

$Sp^3 \rightarrow Sp^2$ in RDS (dissociative)



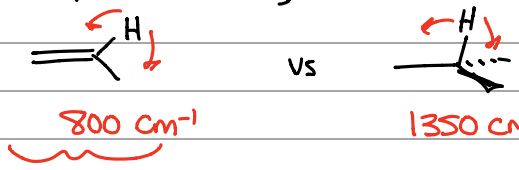
Normal Secondary KIE 1.1 → 1.4 α-KIE

$Sp^2 \rightarrow Sp^3$ in RDS (associative)



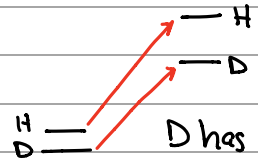
$\frac{k_H}{k_D} = 0.73$ Inverse Secondary KIE <1 Commonly 0.8 → 0.9

* The out of plane bending dominates the secondary KIE



800 cm^{-1} 1350 cm^{-1}

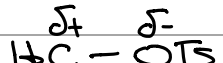
Weaker force constant = smaller C-H / C-D Gap

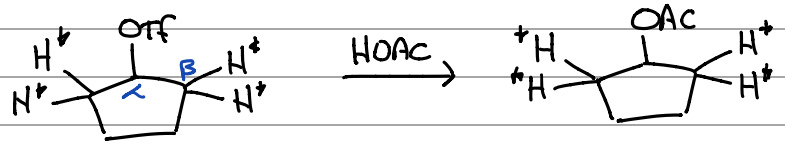


D has smaller barrier

$\frac{k_H}{k_D} = 0.96$

α - inverse secondary KIE





$\frac{k_H}{k_D} = 2.06$

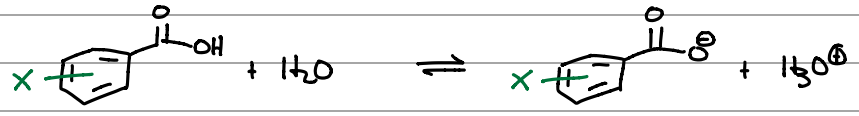
β - normal secondary KIE

Linear Free Energy Relationships (LFER)

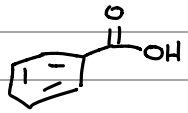
Goal: Study how substituents influence the rate or equilibrium of a rxn.

Hammett Plots

- Scale to measure the ability of substituents to influence the acidity of benzoic acid



X = meta or para



pKa 4.21

pKa 4.48

$\sigma = -0.27$

pKa 3.44

$\sigma = 0.77$

Substituent parameter (σ) for each substituent

↳ For Ph-COOH $\sigma_H = 0$

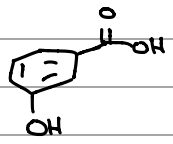
$$\sigma_x = \log \frac{K_x}{K_H} = pKa(H) - pKa(X)$$

When $\sigma = \ominus$	X = EDG	Less acidic than PhCOOH
When $\sigma = \oplus$	X = EWG	More acidic than PhCOOH

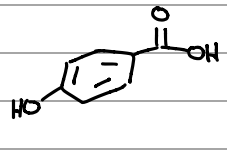
For PhCOOH $\sigma_{para} > \sigma_{meta}$

↑ inductive effect

↳ inductive & resonance effect



$\sigma = 0.13$



$\sigma = -0.38$

Rho (ρ)

- Using PhCOOH as a reference rxn that creates a $\ominus$ charge (→ in H_2O)
- Compare other rxn to see if it involves a $\oplus$ or $\ominus$

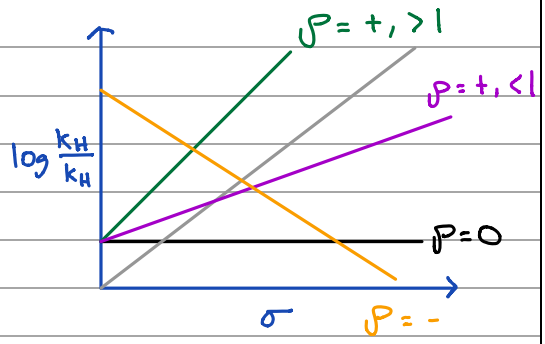
Hammett Relationships:

$\log \frac{K_X}{K_H} = \rho\sigma$ or $\log \frac{k_X}{k_H} = \rho\sigma$

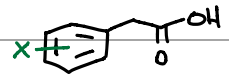
Plot $\log \frac{k_X}{k_H}$ versus σ and ρ = slope

ρ describes the sensitivity of the new rxn to substituent effects.

	Sensitivity to substituent Relative to PhCOOH	Charge Buildup During Rxn
$\rho > 1$	more	$\ominus$
$0 < \rho < 1$	less	$\ominus$
$\rho \approx 0$	no sub. effect	
$\rho < 0$	—	$\oplus$



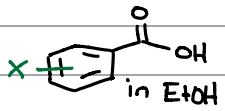
Ex 1



$\rho = 0.56$

Substituents more remote to the COOH group

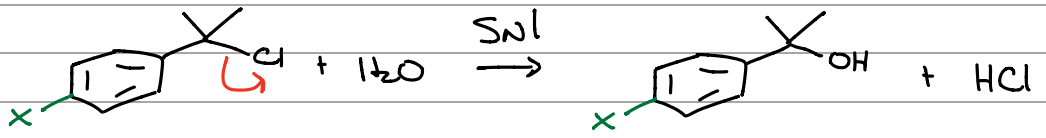
Ex 2

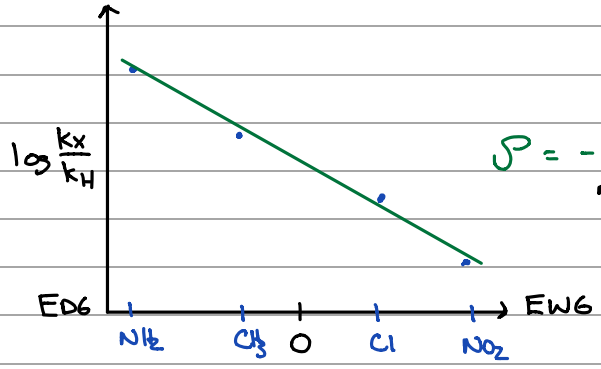


$\rho = 2.25$

Using EtOH makes $\ominus$ less stabilized than when in H_2O = enhanced sensitivity

Ex 3

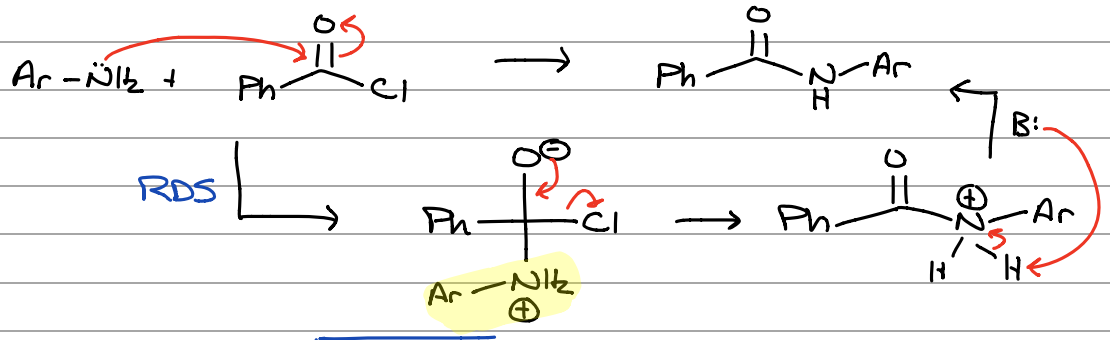




$\rho = -4.38$

$\oplus$ Charge develops in RDS

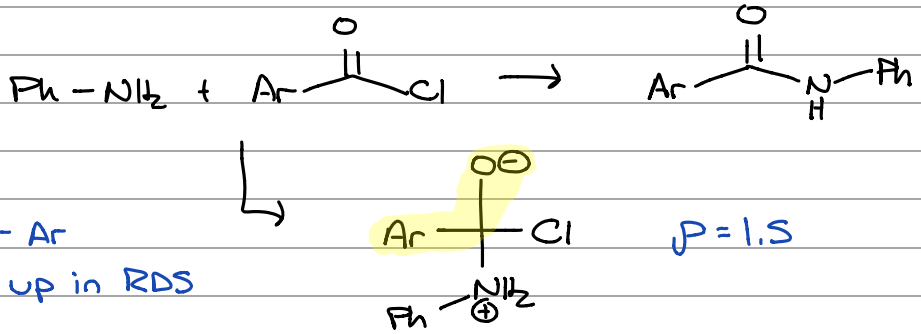
Ex 4



⊕ Near Ar
Builds up in RDS

$\rho = -3.21$

Ex 5

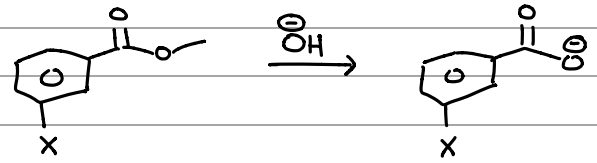


⊖ Near Ar
Builds up in RDS

$\rho = 1.5$

Ex 6

Estimate K when $X = NO_2$ $\sigma = 0.71$



$\rho = 2.38$

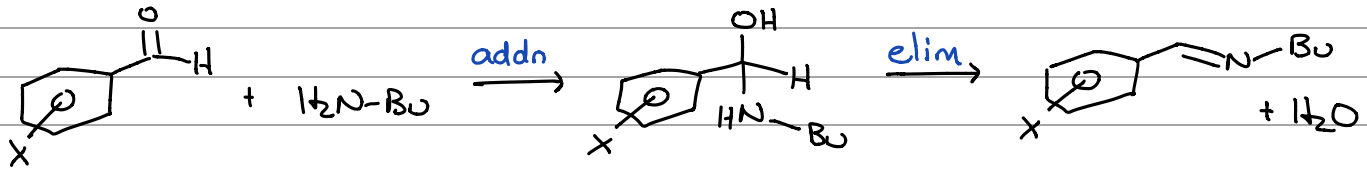
$k_H = 2 \times 10^{-4}$ m/s

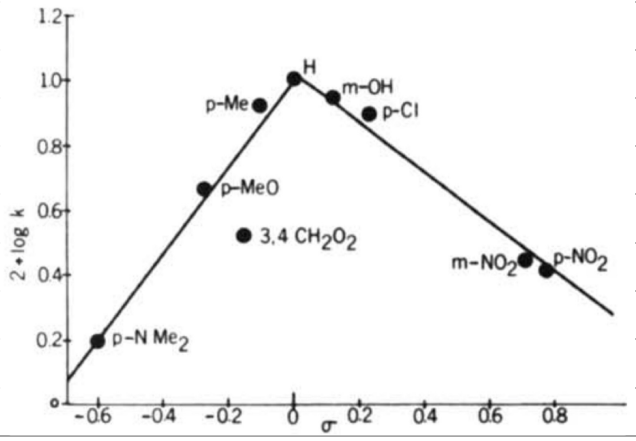
$$\log \frac{k_X}{k_H} = \rho\sigma \Rightarrow \frac{k_X}{k_H} = 10^{\rho\sigma} \Rightarrow k_X = 10^{\rho\sigma} \cdot k_H$$

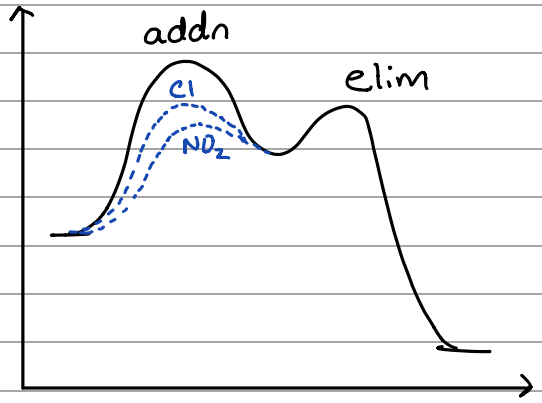
$$= 10^{(2.38 \times 0.71)} \cdot 2 \times 10^{-4} \text{ m/s}$$

$$= 9.8 \times 10^{-3} \text{ m/s}$$

A non-linear plot can indicate change in mechanism or RDS.





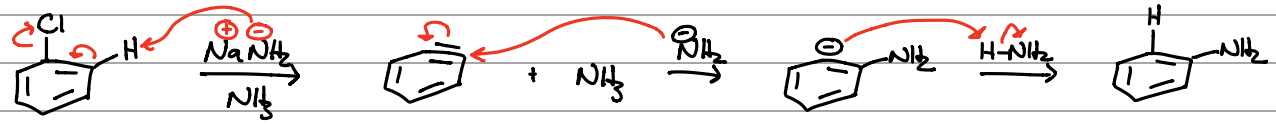


With EWG, the elimination becomes the RDS.

Other Tools for Mechanism Determination

1. Identify all products

2. Intermediate Trapping

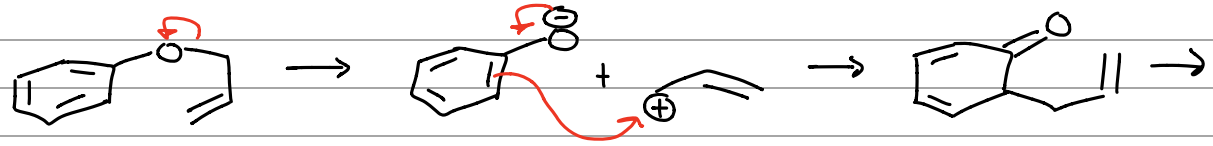


trap with furan

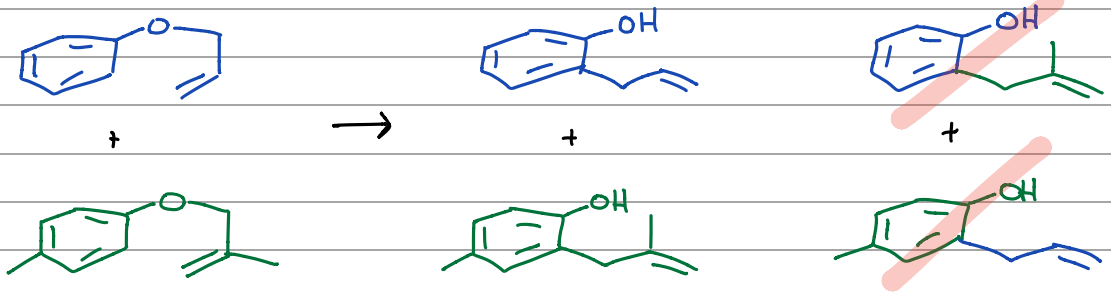
3. Crossover Experiment
   - Use to see if a reactant breaks apart before recombining to give a product.

Claisen Rearrangement

Path B



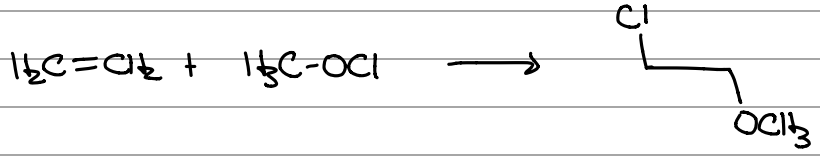
Experiment:

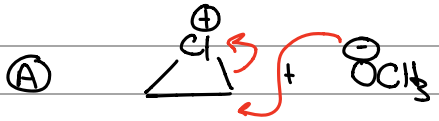


* Must operate via a Concerted mechanism

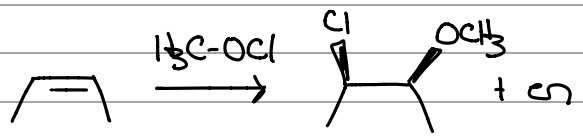
Crossover Products Not Formed

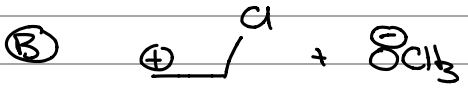
4. Stereochemical Analysis



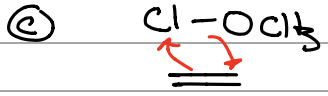


Experiment:

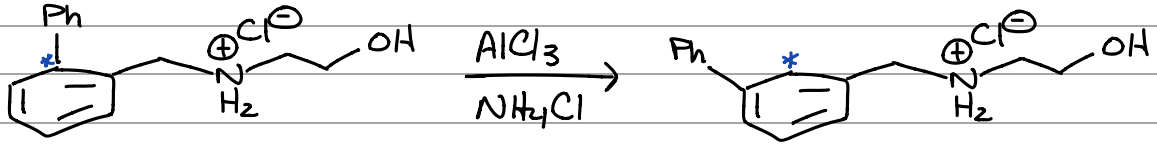




Consistent with mechanism C

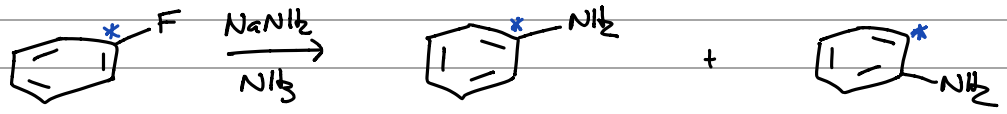


5. Isotope Tracing



Which substituent migrated?

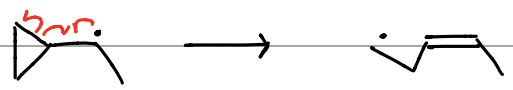
Benzyne:

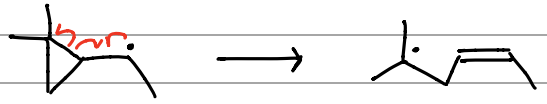


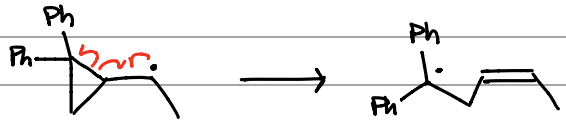
6. Radical Clocks + Traps

- Used to trap a suspected radical intermediate

Newcomb
Tetrahedron 1993 1151

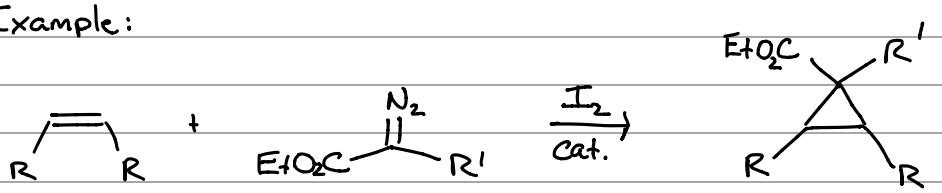


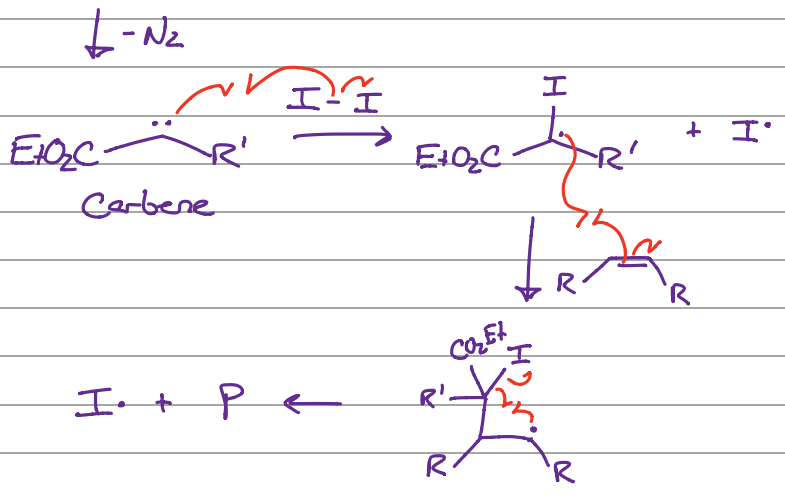




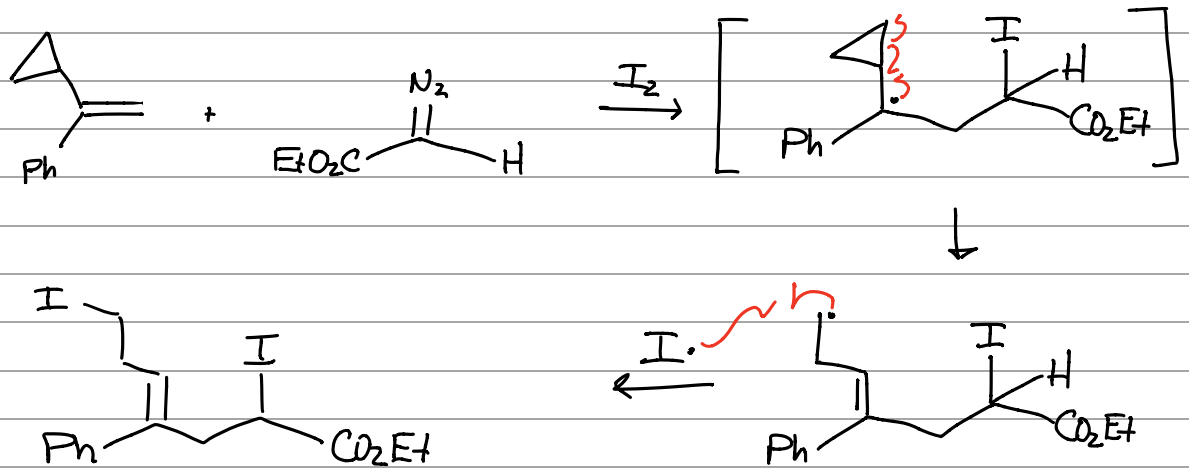
Example:

Nature 2018
1972





Used Cyclopropone as a radical trap



Radical / Cation Trap Newcomb JACS 1994 9753