Kinetic Isotope Effects

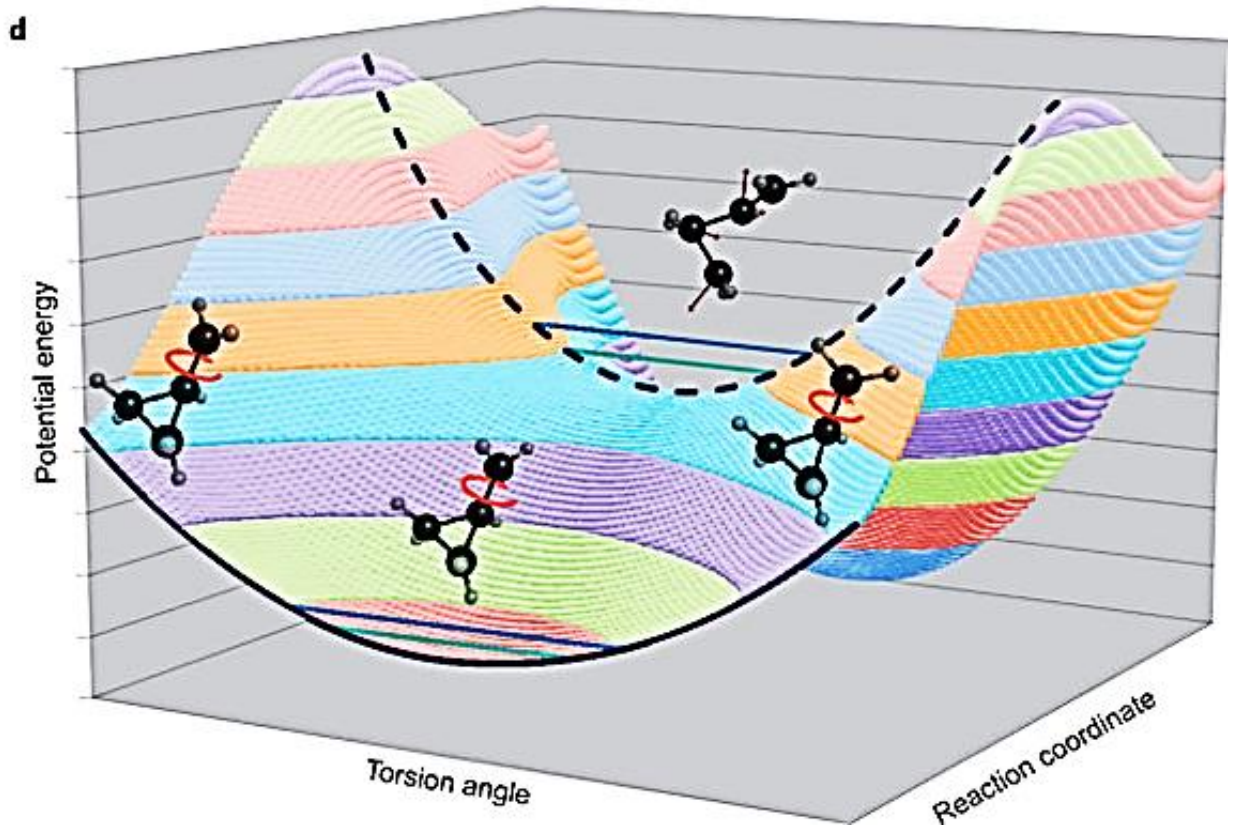
The Study of Organometallic Reaction Mechanisms

Alexander J. Kendall – D.R. Tyler Group Meeting – 7/23/2014

Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev*. **2011**, *111*, 4857-4963.

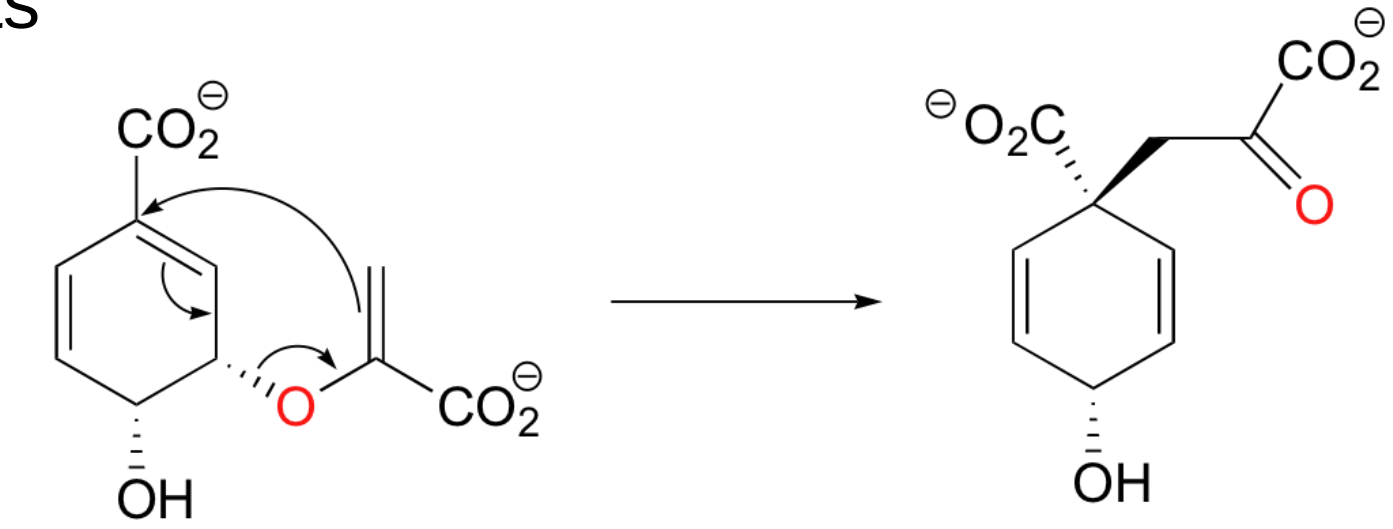
Outline

- General physical organic mechanism investigation
- Kinetic isotope effect (KIE)
  - Origins of the effect
  - Types of KIEs
    - Primary
    - Secondary
    - Equilibrium
    - Solvent
    - Quantum tunneling
    - Steric
  - Magnitude factors in KIE
  - Organometallic studies
    - Early work
    - Misleading results
    - Modern example
- Conclusions



Physical Organic Mechanistic Determination

- Experiments designed to "*unlock the secrets of organic reaction mechanisms*"
- Commonly used experiments
  - Kinetic studies
  - Reactivity trends
  - Stereochemical studies
  - Isotopic tracers
  - Substituent effects
  - Radical clocks
  - Crossover experiments
  - Kinetic isotope effects



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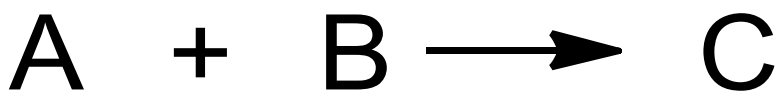
Blum, S. A.; Tan, K. L.; Bergman, R. G. *J. Org. Chem*. **2003**, *68*, 4127-4137.
Goerisch, H. *Biochemistry*, **1978,** *17*, 3700.

Physical Organic Mechanistic Determination



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- **Law of Mass-Action (1864)**
  - experimental determination of reaction rates
  - rate laws and rate constants can be derived
  - $rate = k[A]^n[B]^m$
- **Arrhenius Equation (1889)**
  - $k = \mathrm{A}e^{-Ea/(RT)}$
  - E_a = Energy/mol of kinetic barrier
- **Eyring Equation (1935)**
  - $k = \frac{k_B T}{h}(e^{\Delta S^{\ddagger}/R})(e^{-\Delta H^{\ddagger}/RT})$
  - Energy in entropy and enthalpy

C.M. Guldberg; P. Waage *C. M. Forhandlinger: Videnskabs-Selskabet i Christiana*, **1864**, 35. ; P. Waage *Forhandlinger i Videnskabs-Selskabet i Christiania*, **1864,** 92. ; C.M. Guldberg *C. M. Forhandlinger i Videnskabs-Selskabet i Christiania* **1864**, 111. ; Arrhenius, S.A. *Z. Physik. Chem.* **1889**, *4*, 96–116. ; Arrhenius, S.A. *ibid.* **1889**, *4,* 226–248. ; Eyring, H. *J. Chem. Phys.* **1935**, *3,* 107.

Physical Organic Mechanistic Determination

- **Observe trends in reactivity**
  - Intermediates can be inferred
  - Limits of reactivity book-end

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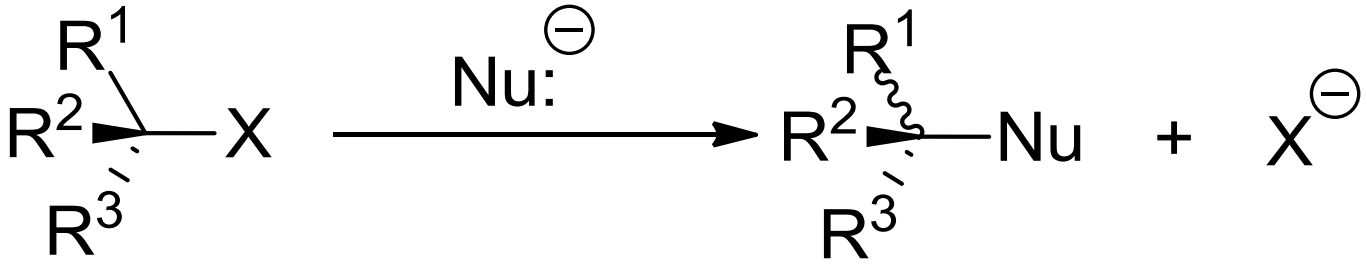

S_N1: Nu = weak

$3^o > 2^o >> 1^o$

S_N2: Nu = strong

$1^o > 2^o >> 3^o$

Blum, S. A.; Tan, K. L.; Bergman, R. G. *J. Org. Chem*. **2003**, *68*, 4127-4137.

Physical Organic Mechanistic Determination

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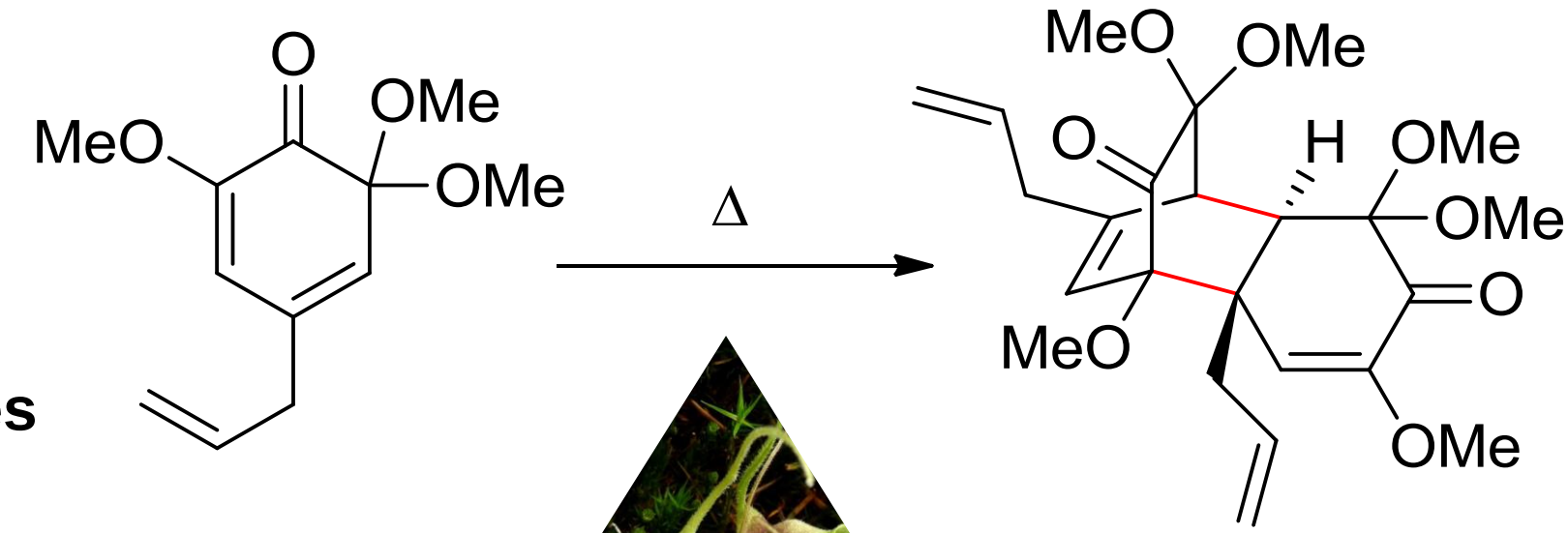

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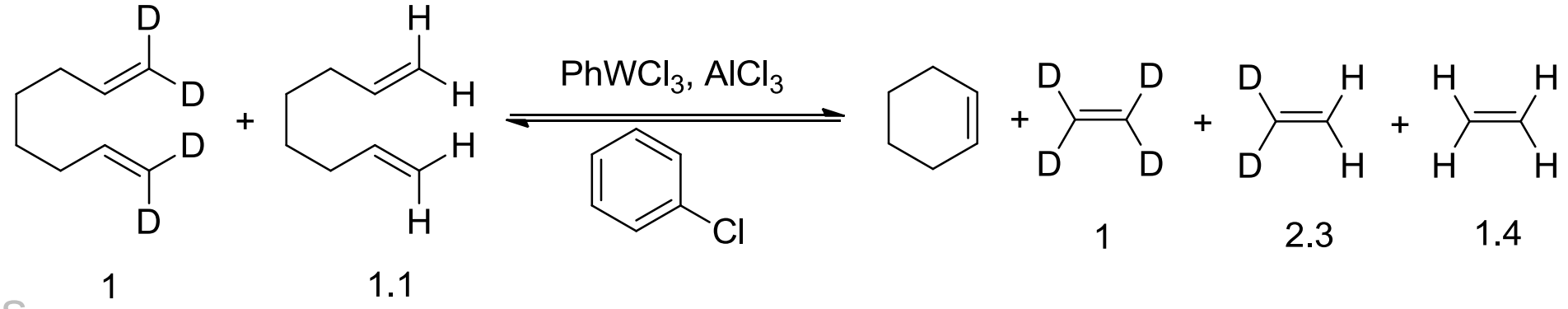
Kurti, L.; Szilagyi, L.; Antus, S.; Nogradi, M. *Eur. J. Org. Chem*. **1999**, 2579-2581.

Physical Organic Mechanistic Determination



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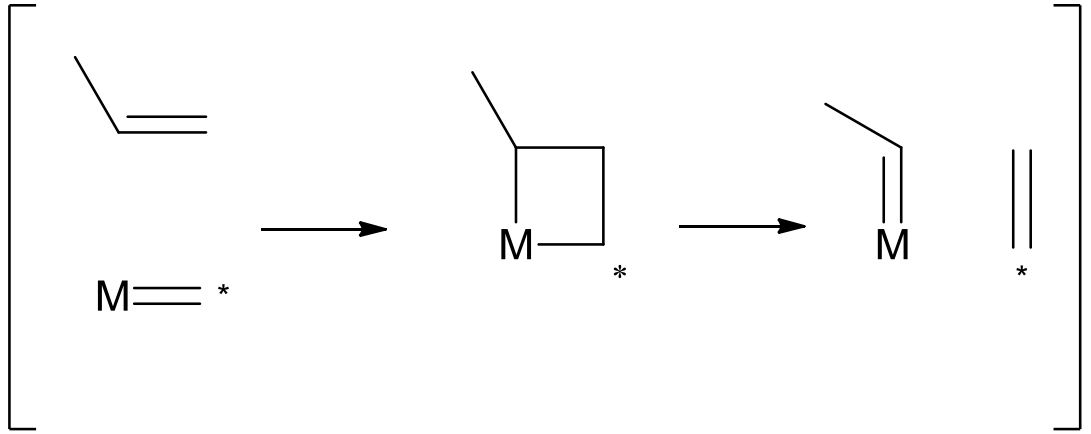

2005 Nobel Prize in Chemistry

Grubbs, Robert H.; Burk, Patrick L.; Carr, Dale D. *J. Am. Chem. Soc.* **1975**, *97*, 3265–3267.

Physical Organic Mechanistic Determination

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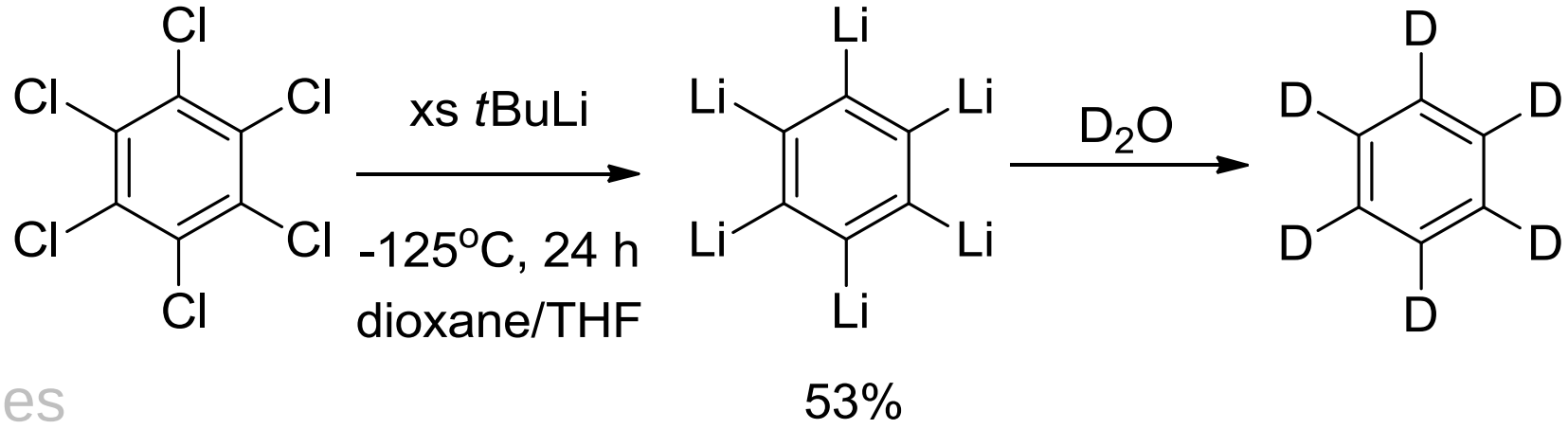

53%

- **Structure assignment**
  - Trap out reactive sites to prove where they were generated *in-situ*

Baran, J. R.; Hendrickson, C.; Laude, D. A.; Lagow, R. J. *J. Org. Chem.* **1992**, *57*, 3759-3760.

Physical Organic Mechanistic Determination

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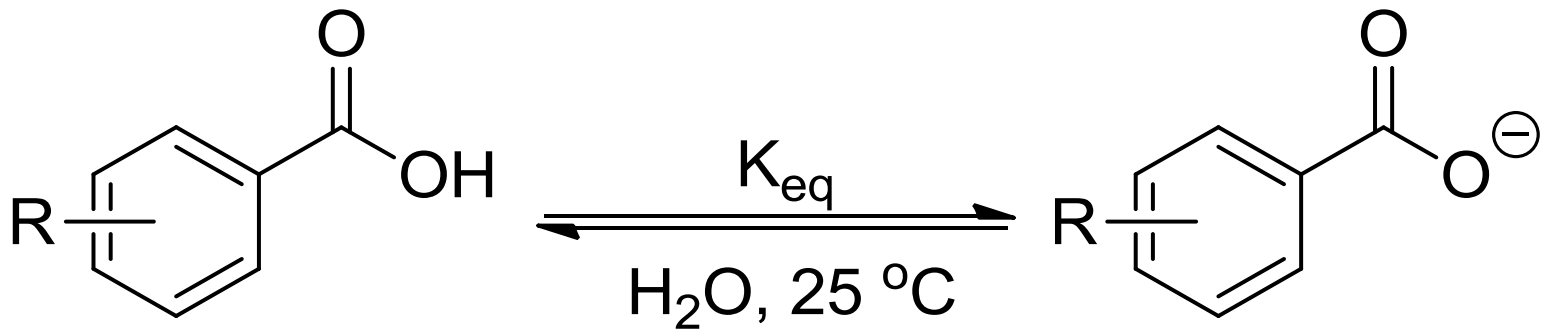

- **Hammet Equation (1937)**
  - $\log(\frac{K}{K_0}) = \sigma\rho$
  - σ = substituent constant
  - ρ = reaction constant

Hammett, Louis P. *J. Am. Chem. Soc.* **1937**, *59*, 96.

Physical Organic Mechanistic Determination

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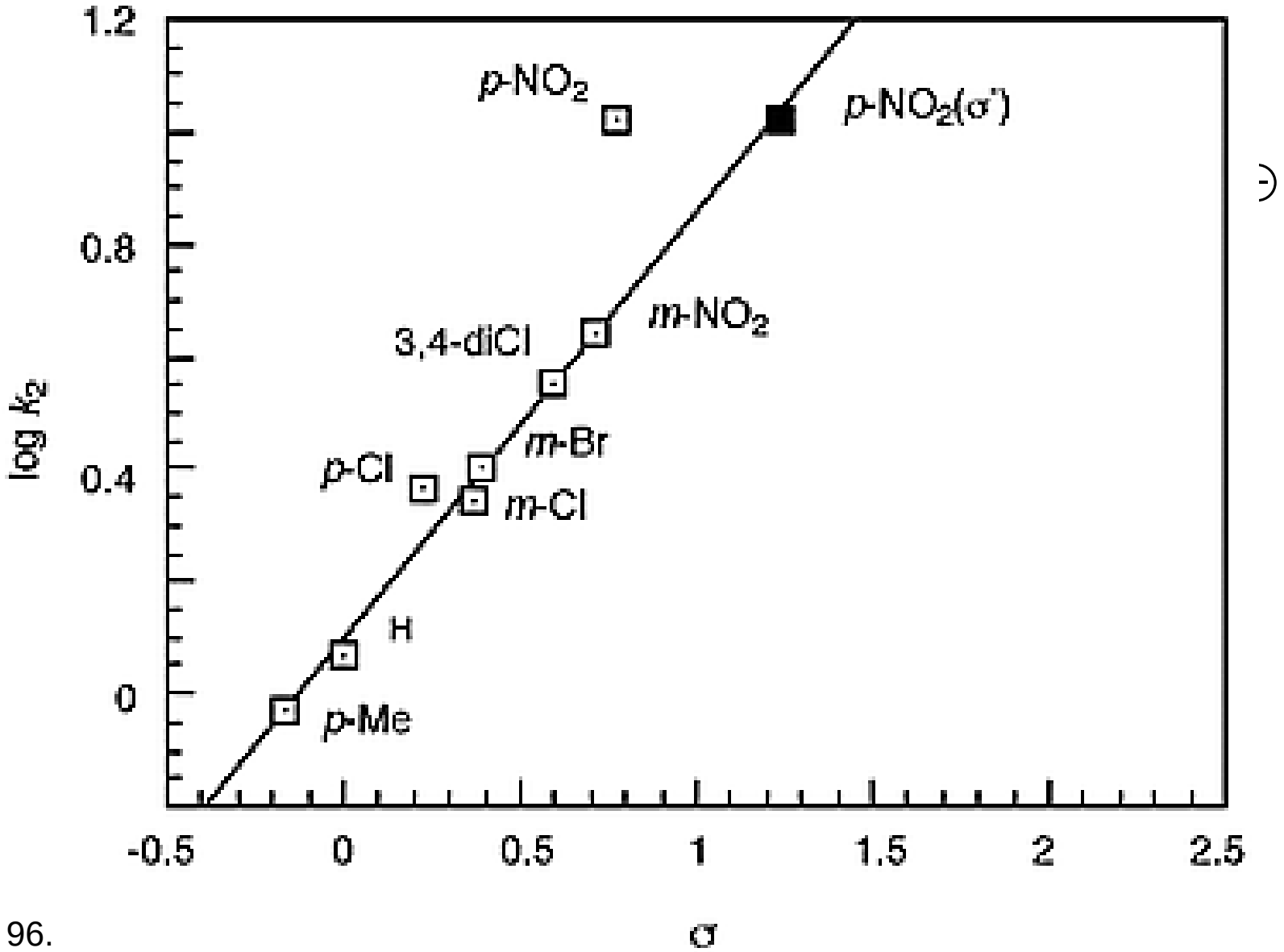

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Physical Organic Mechanistic Determination

- Kinetic studies
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- **Radical clocks**
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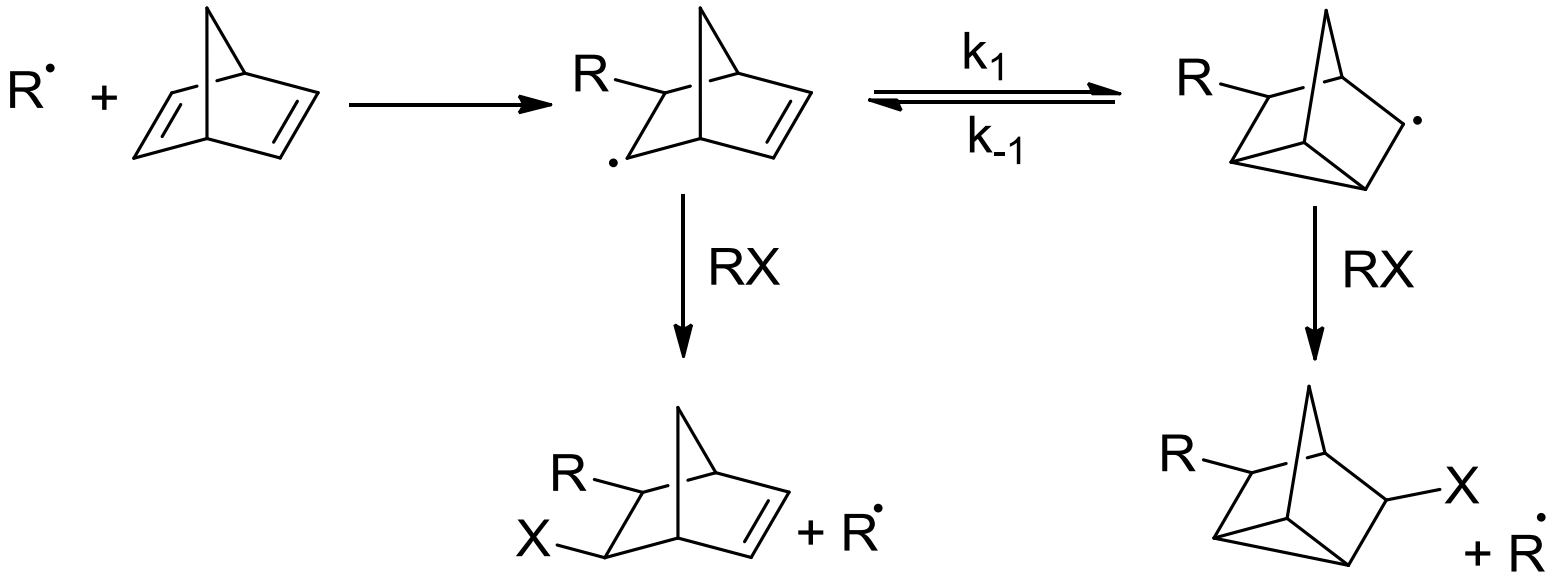
- **Radical clocks**
  - Use competing uni-molecular radical reactions as qualitative timing devices to investigate the rates of radical-molecule reactions



Griller, D.; Ingold, K. U. *Acc. Chem. Res*. **1980**, *13*, 317-323.

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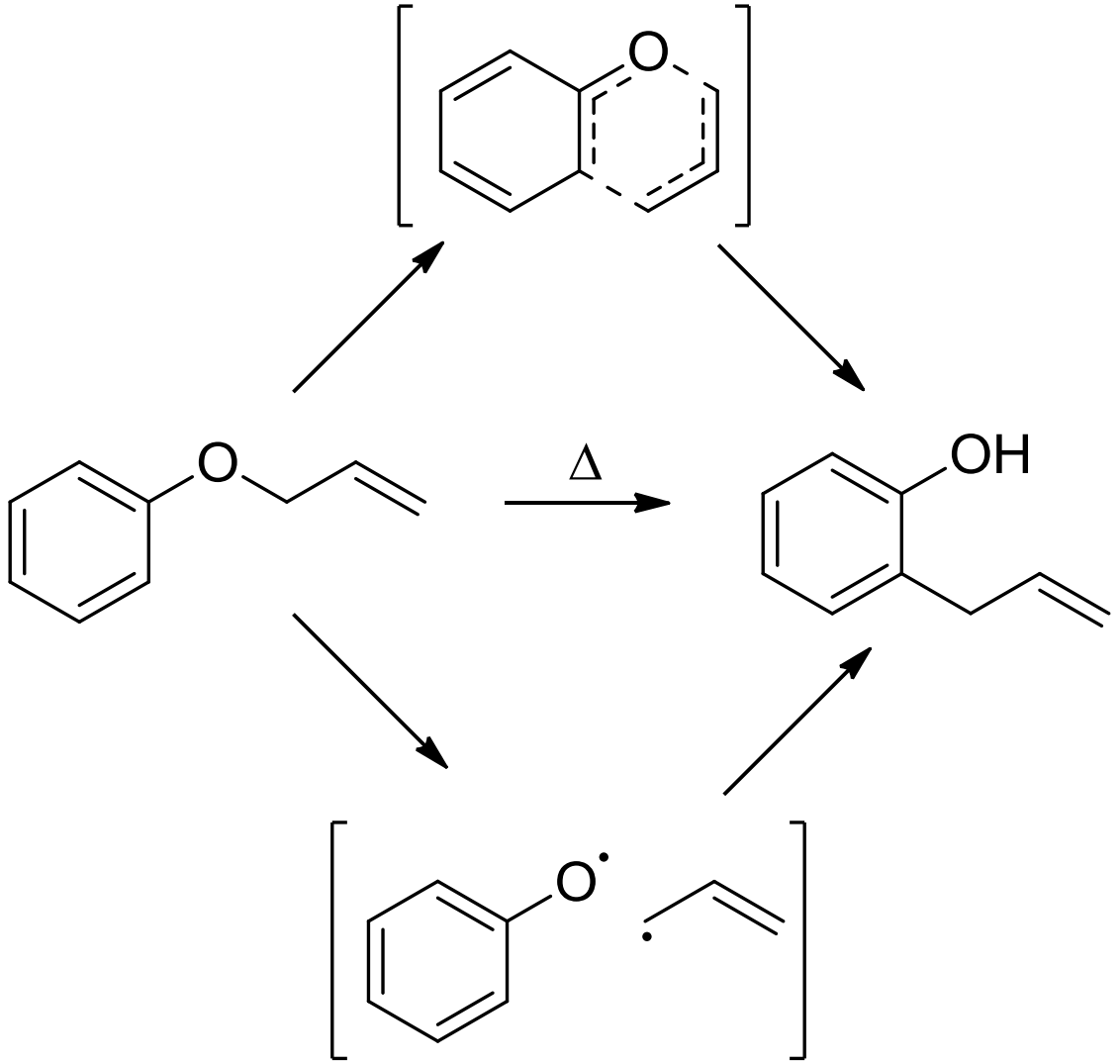

Carroll, Felix A.; Perspectives on Structure and Mechanism in Organic Chemistry; Brooks/Cole Publishing, Pacific Grove, CA, 1998

Physical Organic Mechanistic Determination

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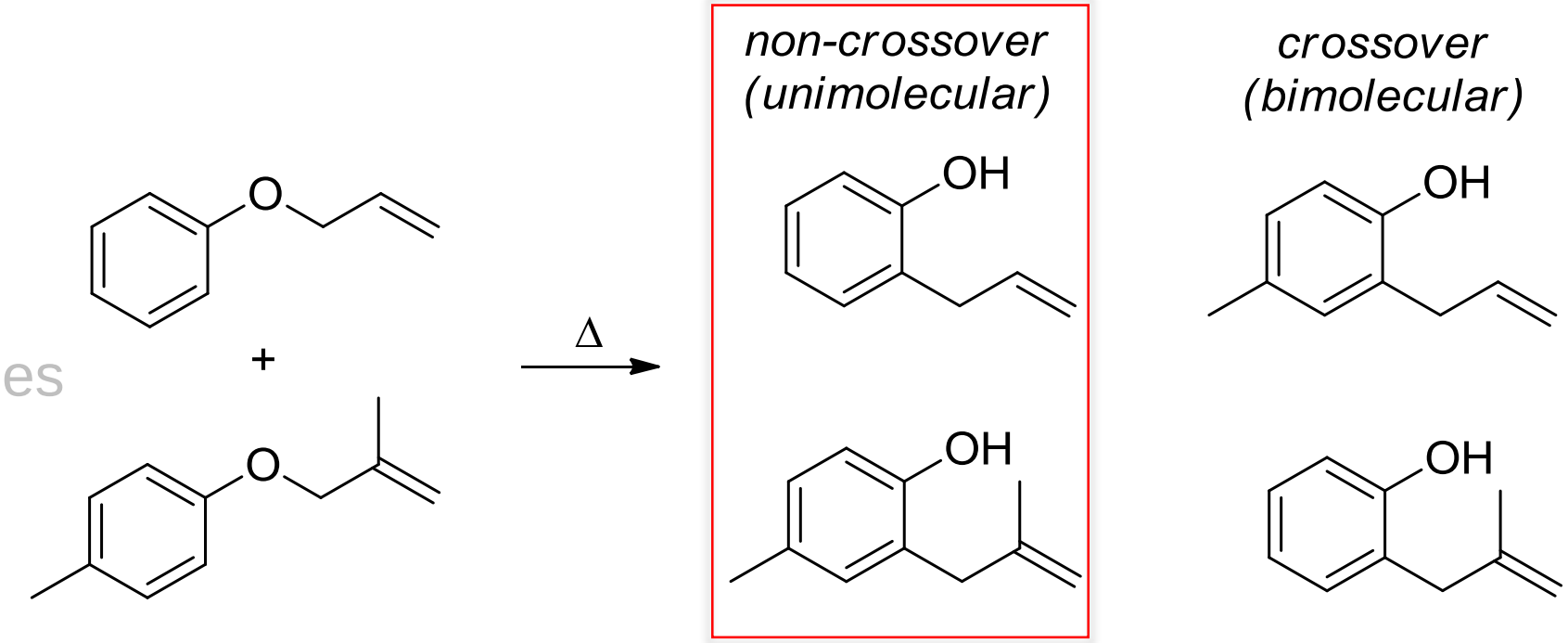

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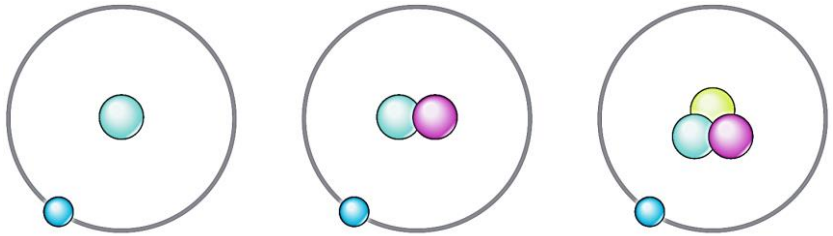
Physical Organic Mechanistic Determination



- Kinetic studies
- Reactivity trends
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- Isotopic tracers
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- Radical clocks
- Crossover experiments
- **Kinetic isotope effects**

- **Isotope effects**
  - Same reaction mechanisms
  - NMR and MS compatible
  - Well established protocols and isotope sources
  - Works well for short-lived RDS intermediates
  - Works well for complex reaction mechanisms
  - Which bonds broken/formed in RDS?

"As the chemistry of the *metal* determines the course of the reaction, the standard approaches of physical organic chemistry are sometimes of little use in the study of insights of the reactions."

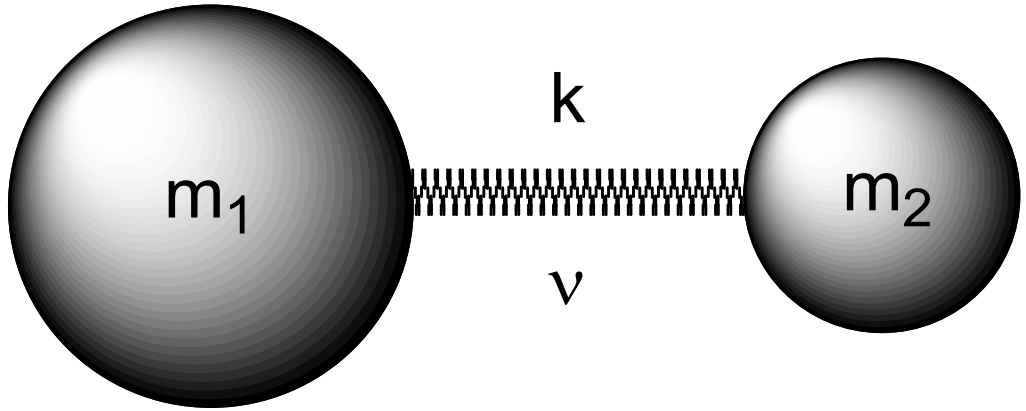
Blum, S. A.; Tan, K. L.; Bergman, R. G. *J. Org. Chem*. **2003**, *68*, 4127-4137.
Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev*. **2011**, *111*, 4857-4963.

Origins of the Kinetic Isotope Effect (KIE)

- All KIEs rely on a difference in zero-point energies

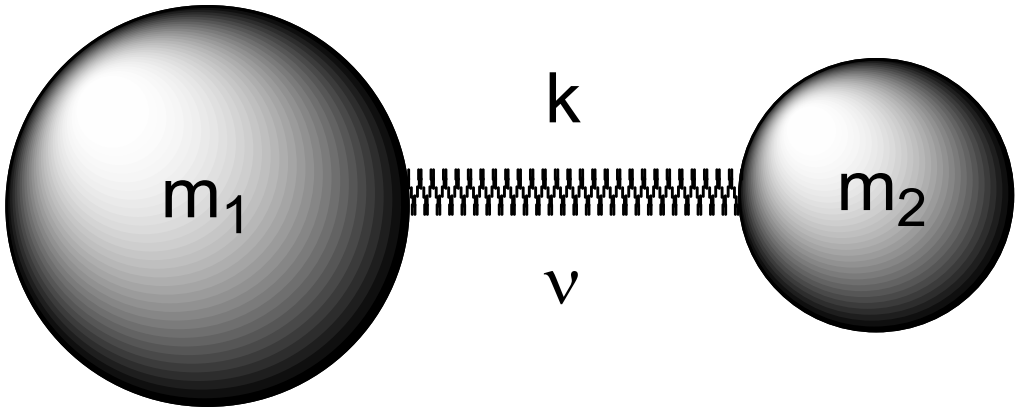
  - $\nu = \frac{1}{2\pi}\sqrt{\frac{k}{m_r}}$

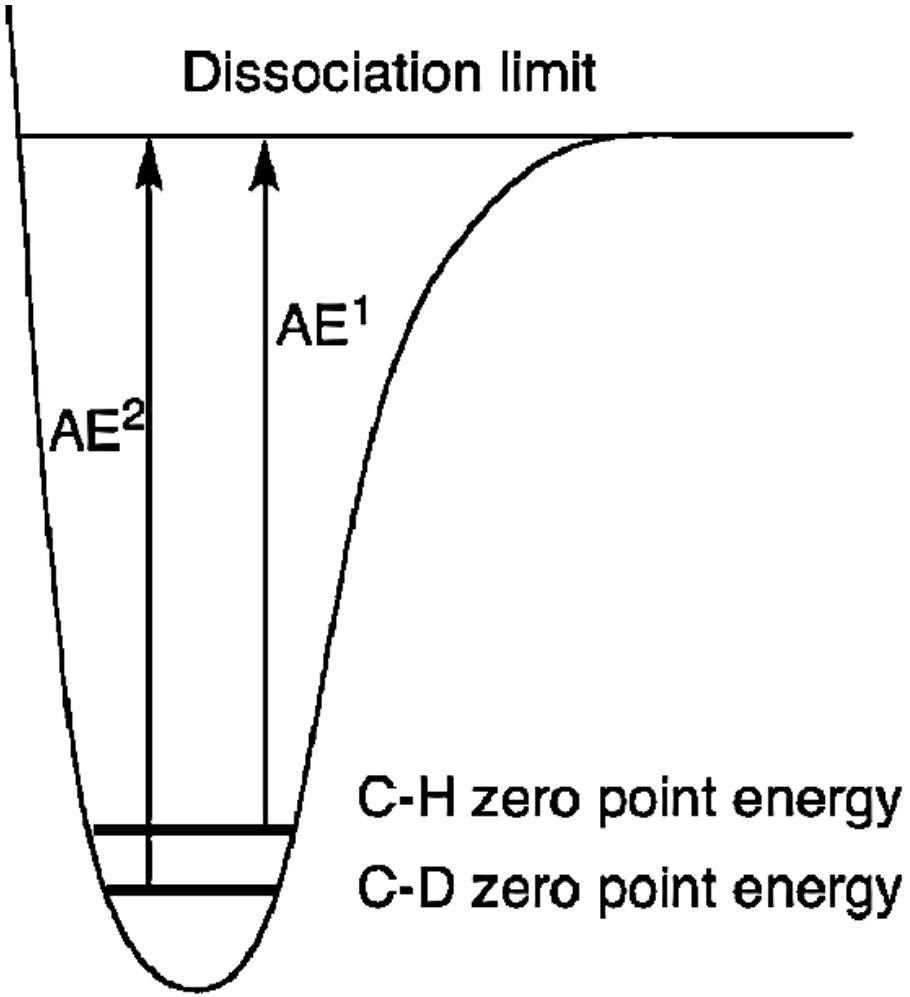
    - v= bond stretching vibration
    - k= bond force constant
    - $m_r = \frac{m_1 m_2}{m_1 + m_1}$



Zero-Point Energy (ZpE)

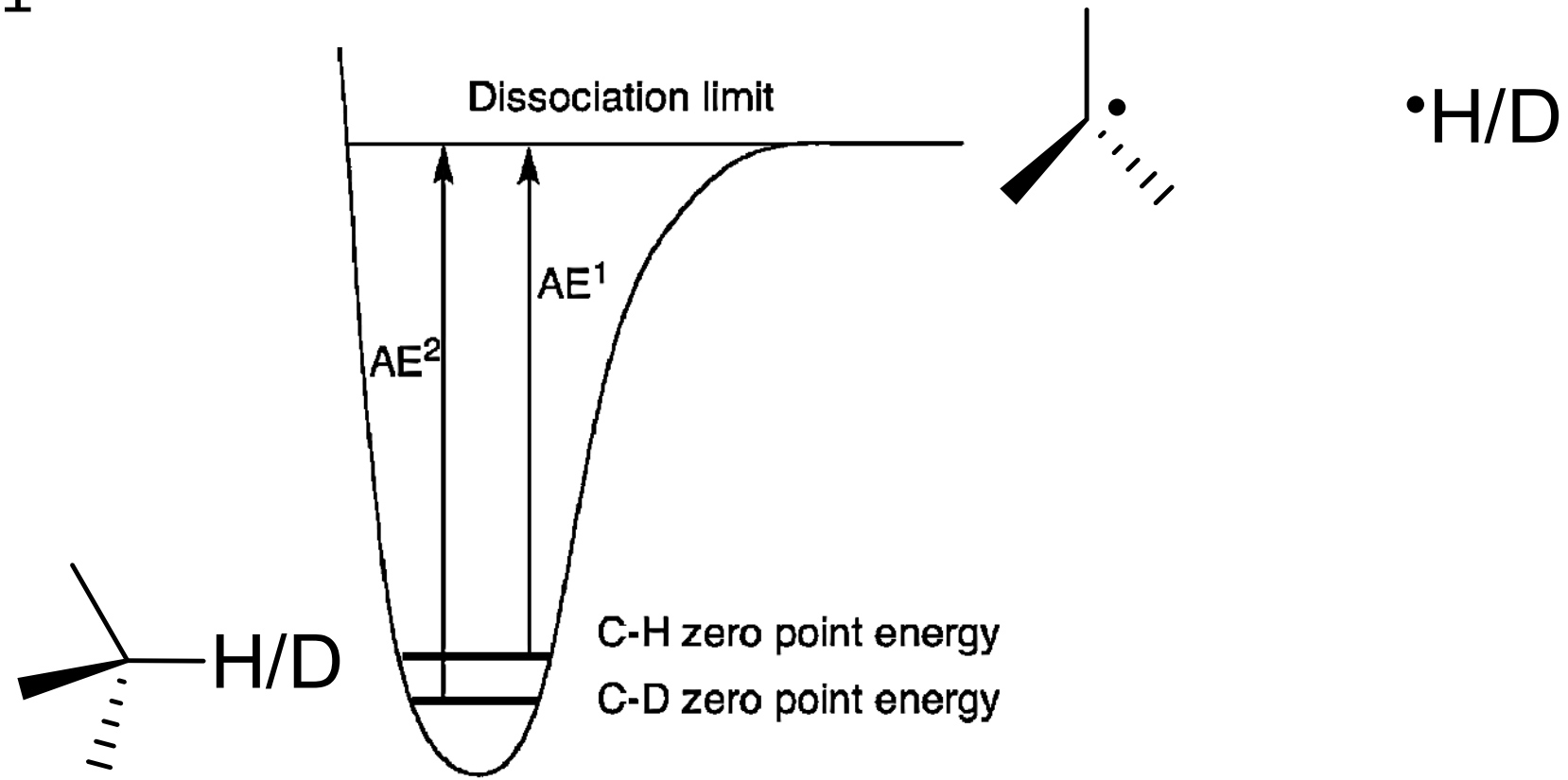
- The result of this mass difference:
  - m_1= C,N,O; m_2= H,D;
  - $k_H/k_D \leq 6.8$ (298K)
    - k_H = rate of reaction with hydrogen
    - k_D = rate of reaction with deuterium
- Heavy isotope effects ($m_2 \neq$ H or D)
  - Much smaller effect due to m_r being very close for heavy isotopes





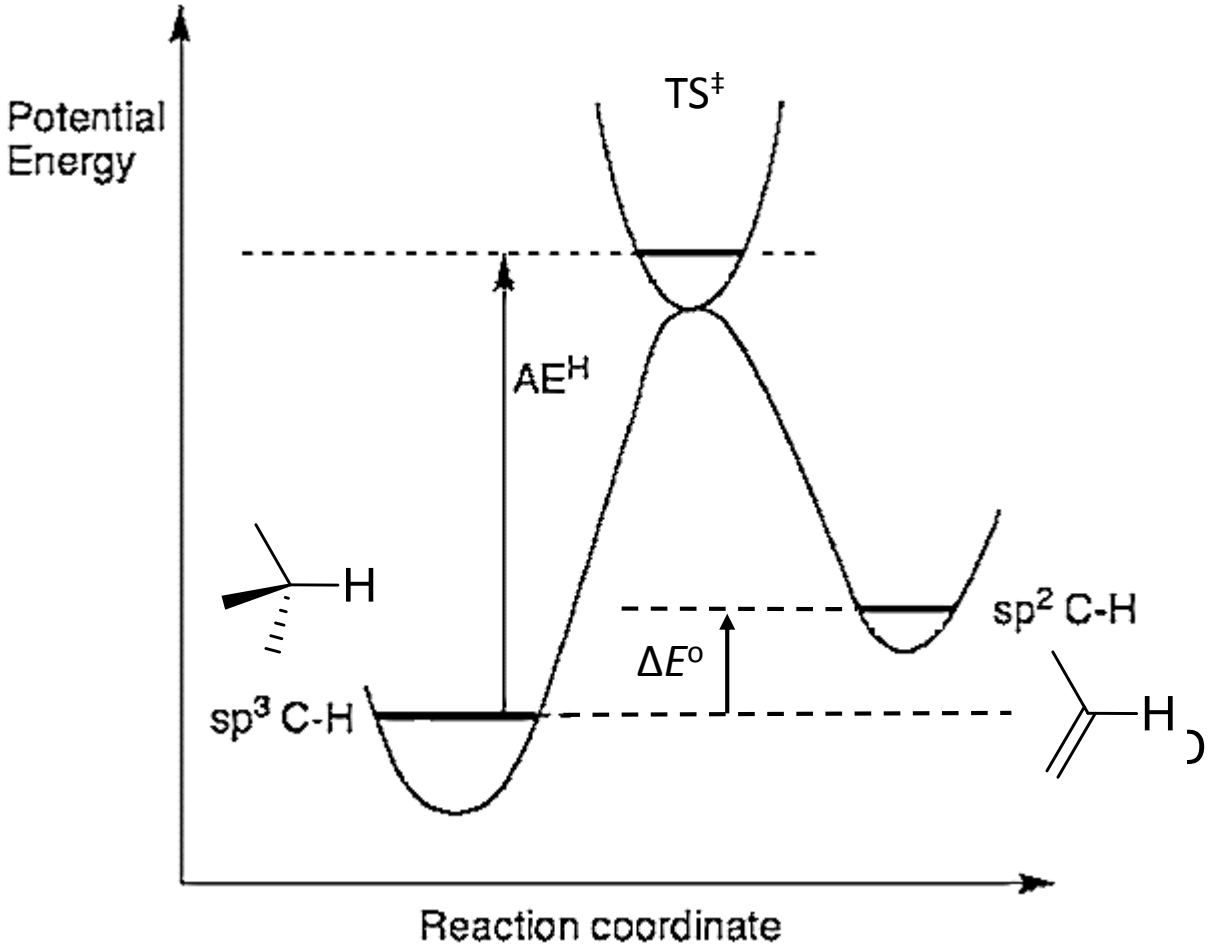
Types of Kinetic Isotope Effects

- Primary isotope effect
  - Isotope replacement has been made in a bond that is broken in the RDS;
  - k_H/k_D >>1



Types of Kinetic Isotope Effects

- Secondary isotope effect
  - Isotope replacement made far from reactive center, or in bonds that only change their hybridization in the RDS;
  - **k_H/k_D ~ 1.2 (*normal*)**
  - k_H/k_D ~ 0.8 (*inverse*)



C-H/D bonds are not being broken during the reaction, but the carbon atoms experience an sp^3 to sp^2 hybridization change.

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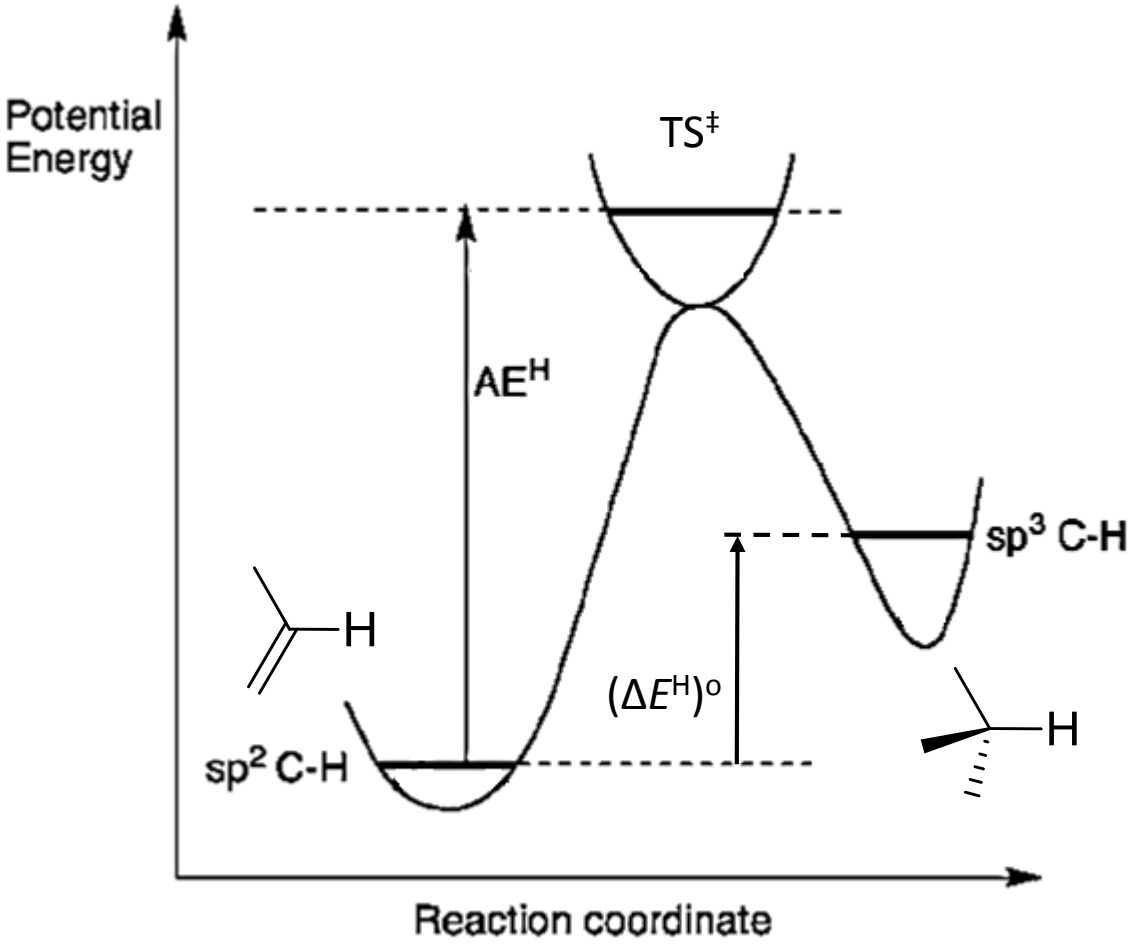


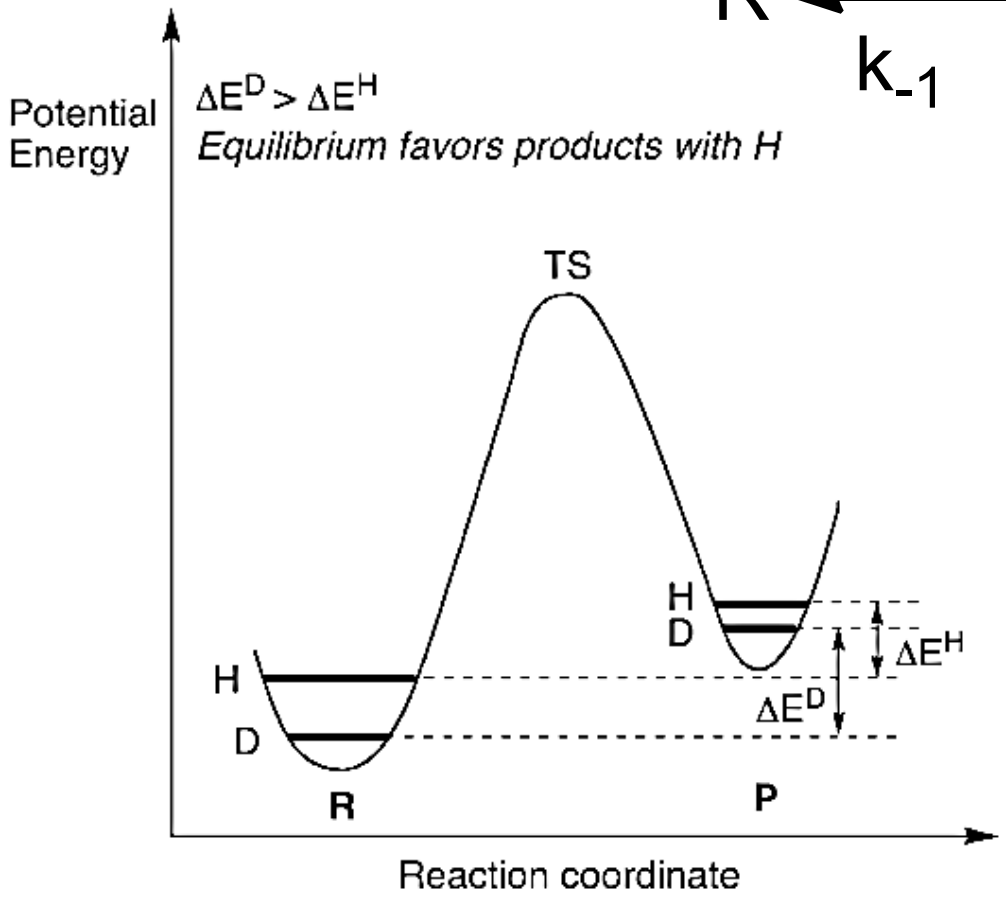
C-H/D bonds are not being broken during the reaction, but the carbon atoms experience an sp^2 to sp^3 hybridization change.

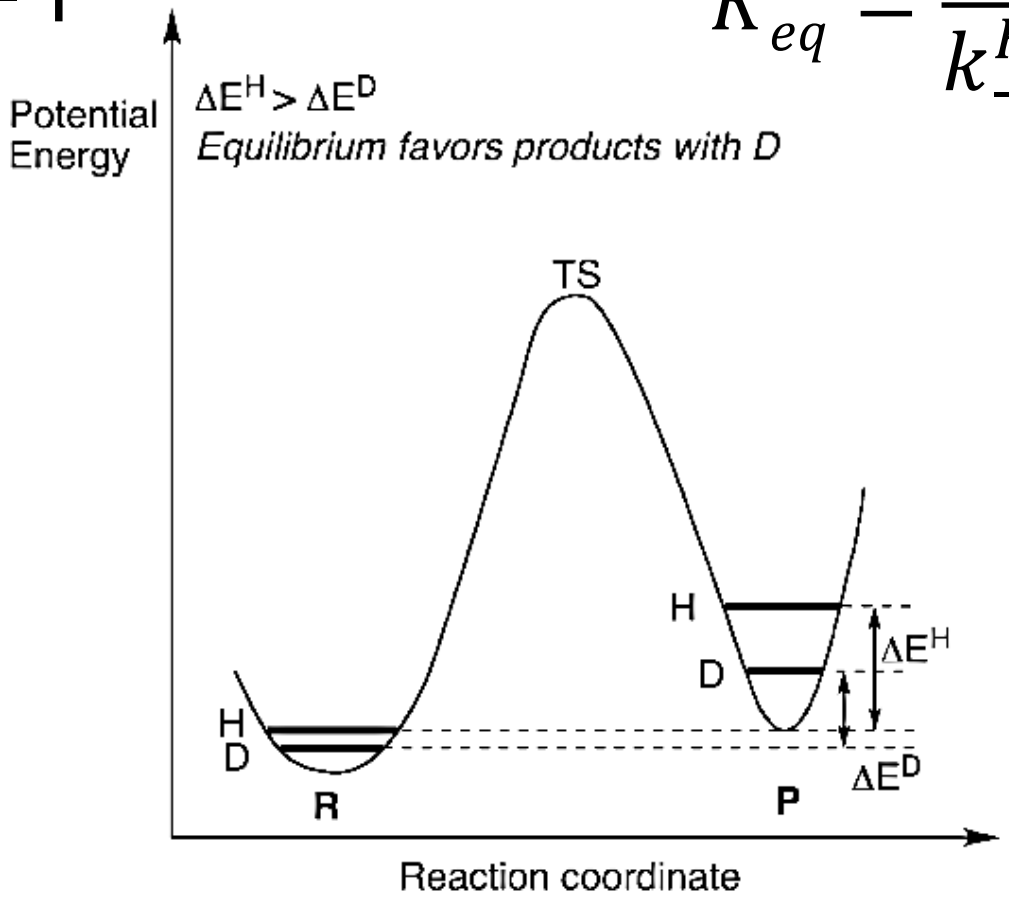
Types of Kinetic Isotope Effects

- Equilibrium isotope effect (a thermodynamic isotope effect)
  - Isotopic change affects the individual rate constants in an equilibrium, modifying K_{eq} values

$$R \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} P$$

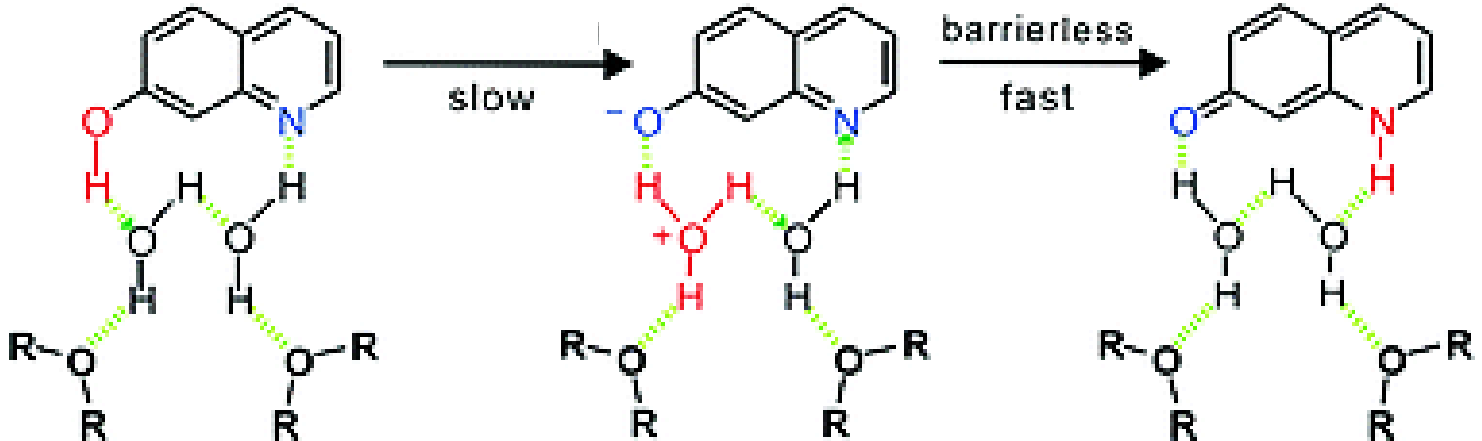
$$K_{eq} = \frac{k_1^H / k_1^D}{k_{-1}^H / k_{-1}^D}$$





Types of Kinetic Isotope Effects

- Solvent isotope effect
  - Kinetic or equilibrium changes observed when the isotopic substitution is made in the reaction solvent (usually H_2O/D_2O)
  - Protic solvents can interchange acidic protons for deuterium
    - *In-situ* isotope labeling
  - Exchangeable proton involved in the RDS = large solvent KIE
  - Differences in the solvation of the activated complex compared to the reactants
  - Hydrogen bonding of the activated complex



Types of Kinetic Isotope Effects

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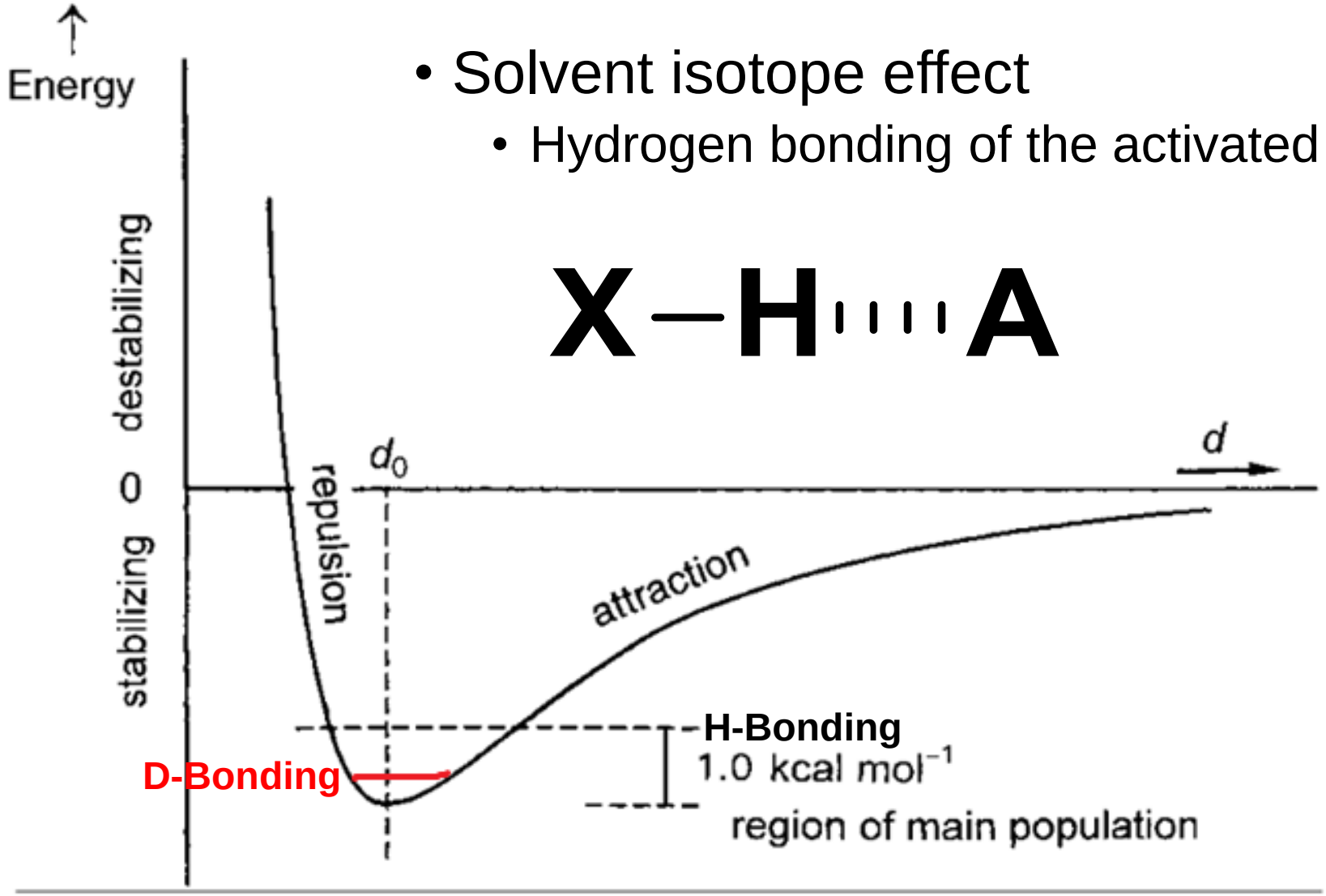
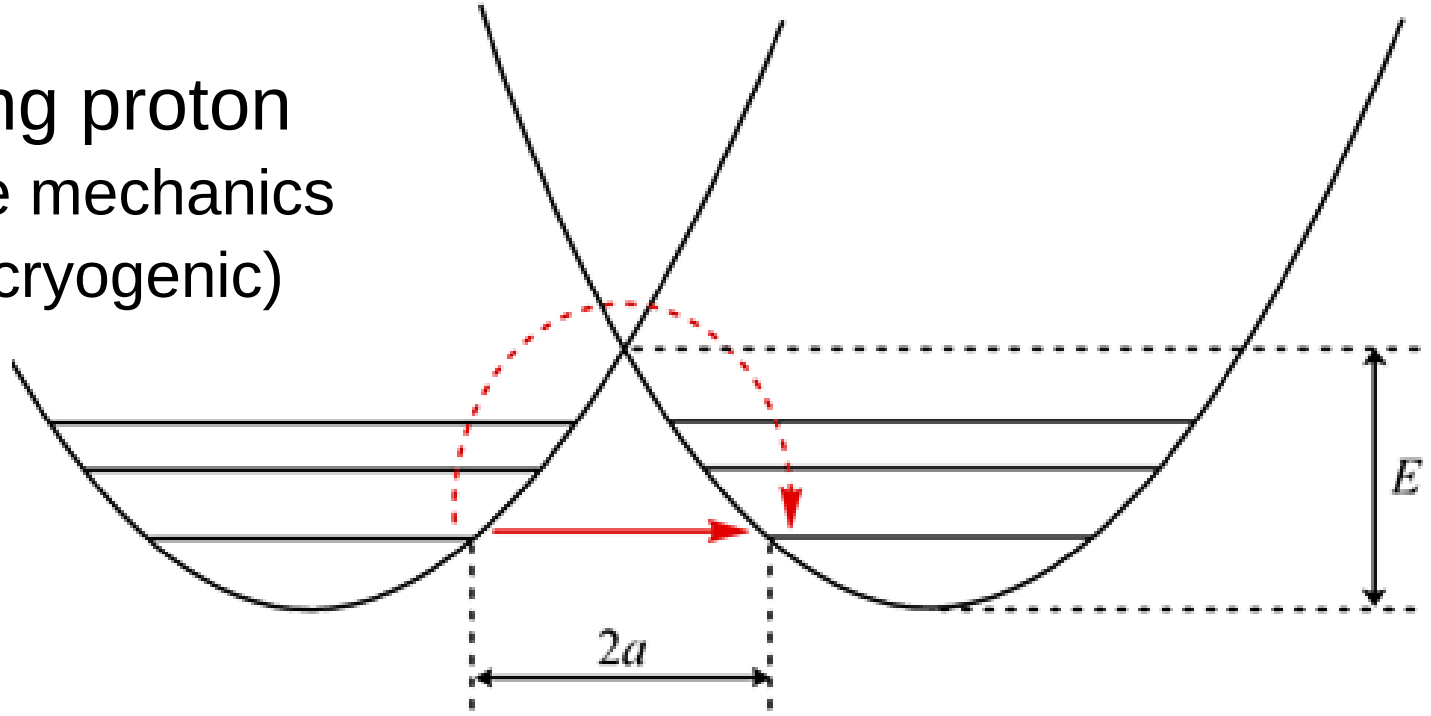


$$X{-}H\cdots A$$

Steiner, T. *Angew. Chem. Int. Ed.* **2002,** *41*, 48-76.

Types of Kinetic Isotope Effects

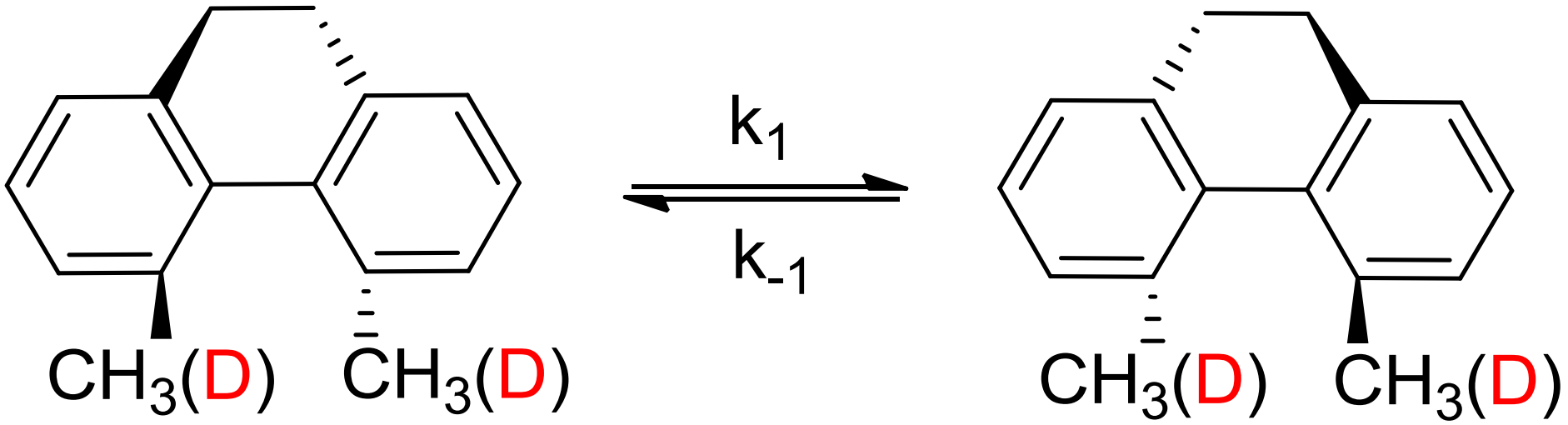
- Quantum tunneling isotope effect
  - If the RDS involves a proton quantum tunneling, an extreme KIE is observed, albeit very rare;
  - k_H/k_D >10
- To tell if you have a tunneling proton
  - Tunneling is caused by wave mechanics
  - Low temperature reactions (cryogenic)
  - Large -$S^{‡}$



Buncel, E.; Lee, C.C. Isotopes in Organic Chemistry. Elsevier: Amsterdam, 1977, Vol. 5.
Krishtalik, L. I. *Biochimica et Biophysica Acta* **2000**, *1458*, 6–27.

Types of Kinetic Isotope Effects

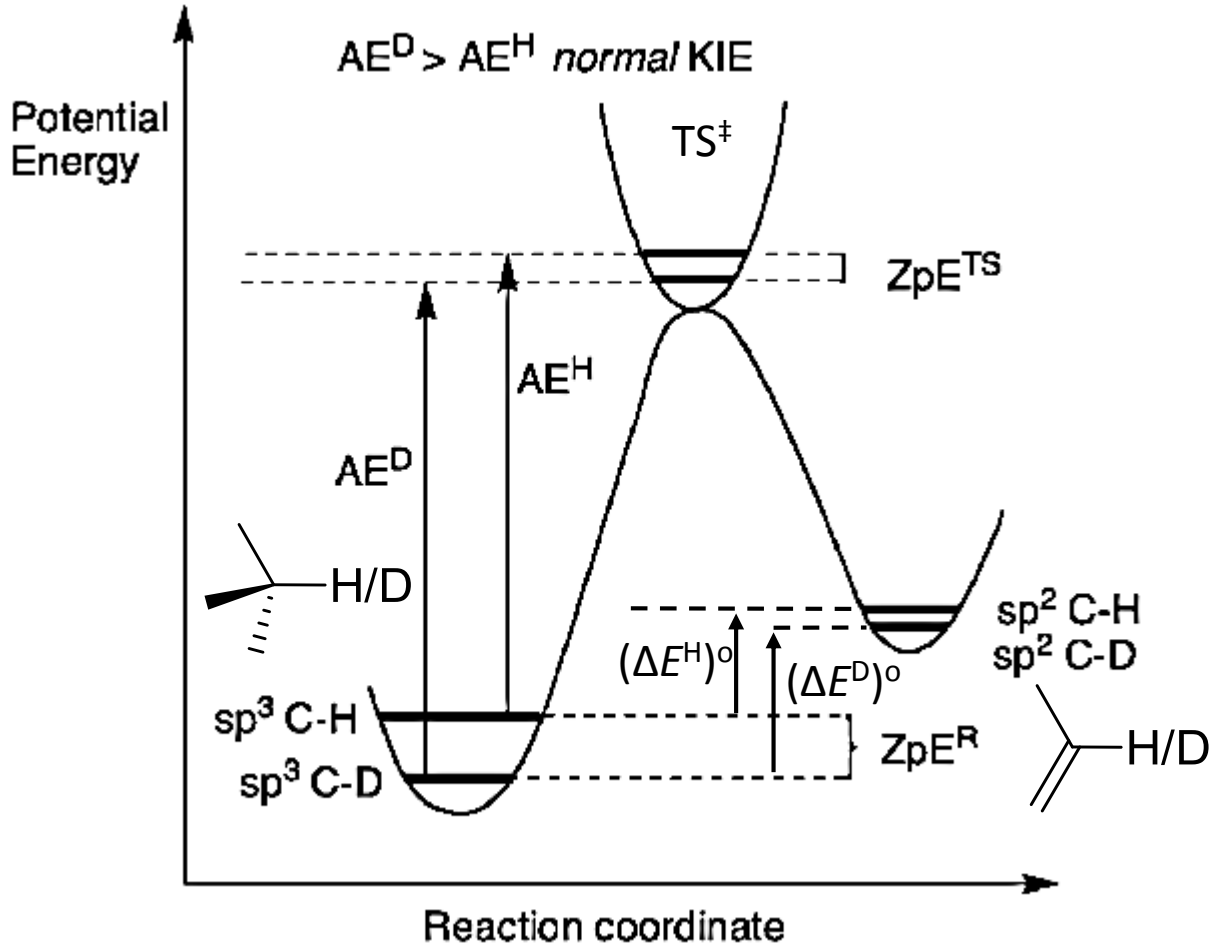
- Steric Isotope Effect
  - k_1^H / k_1^D = 0.88
  - C-D bond shorter than C-H bond
  - D = smaller van der Waals radius (15% smaller than H)
  - $D_2O_{(s)}$ sinks in H_2O



Mislow, K.; Graeve, R.; Gordon, A. J.; Wahl, G. H. *J. Am. Chem. Soc.* **1963,** *85,* 1199–1200.
A. R. Ubbelohde *Trans. Faraday Soc.*, **1936**, *32*, 525-529.

Magnitude of the KIE

- Dependent on ZpE of reactants and ZpE of transition states
- All vibrations for the bonds undergoing transformation contribute to observed KIE
- k_H/k_D values are affected by:
  - Geometry of TS‡,
  - Degree of bond breaking in TS‡,
  - Degree of bond making in TS‡, and
  - Position of the TS‡ in the reaction coordinate (early, middle, or late TS‡

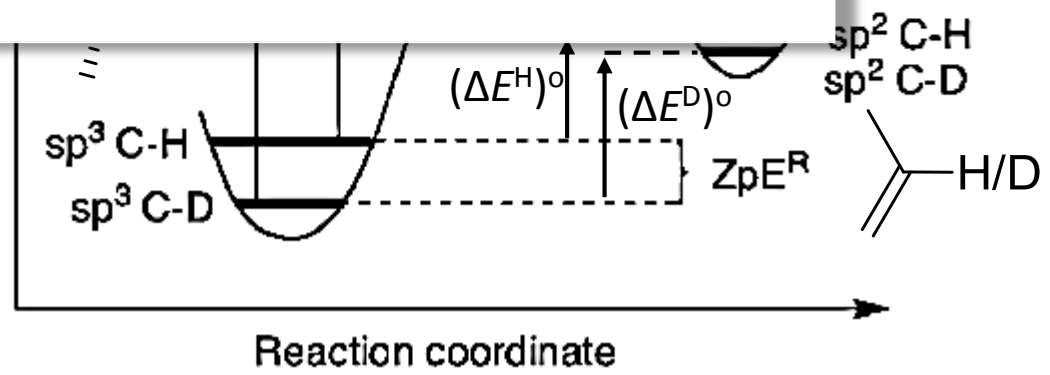


Bigeleisen, J.; Wolfsberg, M. *Adv. Chem. Phys.* **1958**, *1*, 15.

Magnitude of the KIE

- Dependent on ZpE of reactants and ZpE of transition states
- Al
  ob
- k_H
  -
  -
  -
  -

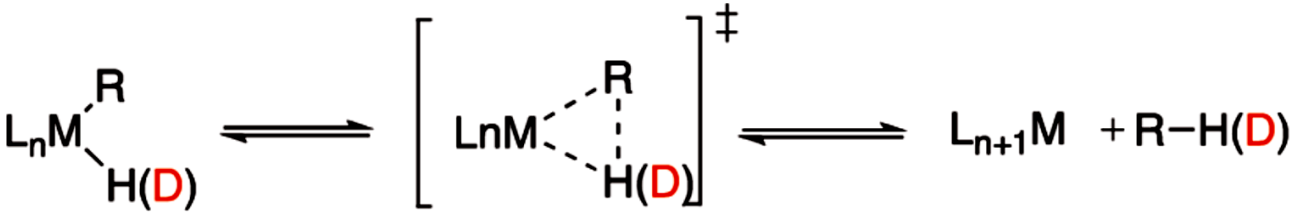
$$\frac{k_H}{k_D} = \left(\frac{s_H^\ddagger s_D}{s_D^\ddagger s_H}\right)\left(\frac{M_H^\ddagger M_D}{M_D^\ddagger M_H}\right)^{3/2}\left(\frac{I_{AH}^\ddagger I_{BH}^\ddagger I_{CH}^\ddagger}{I_{AD}^\ddagger I_{BD}^\ddagger I_{CD}^\ddagger}\frac{I_{AD}I_{BD}I_{CD}}{I_{AH}I_{BH}I_{CH}}\right)^{1/2} \times \left(\frac{\prod_{i=1}^{3N^\ddagger-7}\frac{1-e^{-u_{iD}^\ddagger}}{1-e^{-u_{iH}^\ddagger}}}{\prod_{i=1}^{3N-6}\frac{1-e^{-u_{iH}}}{1-e^{-u_{iD}}}}\right) e^{-1/2\left(\sum_{i=1}^{3N^\ddagger-7}(u_{iH}^\ddagger-u_{iD}^\ddagger)-\sum_{i=1}^{3N-6}(u_{iH}-u_{iD})\right)}$$

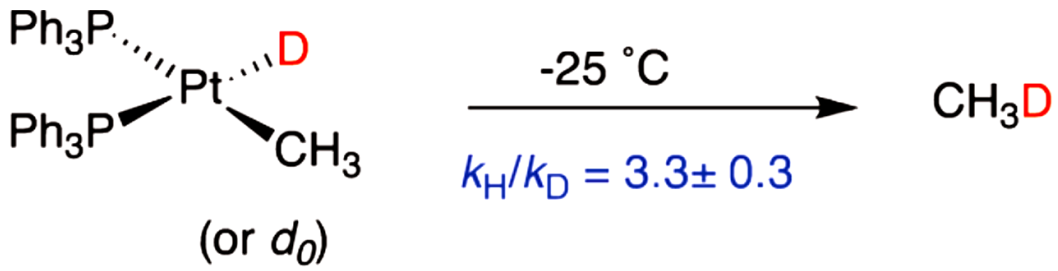


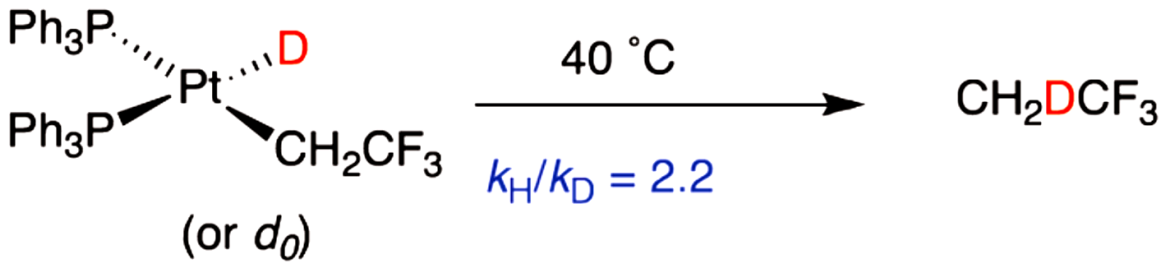
Bigeleisen, J.; Wolfsberg, M. *Adv. Chem. Phys.* **1958**, *1*, 15.

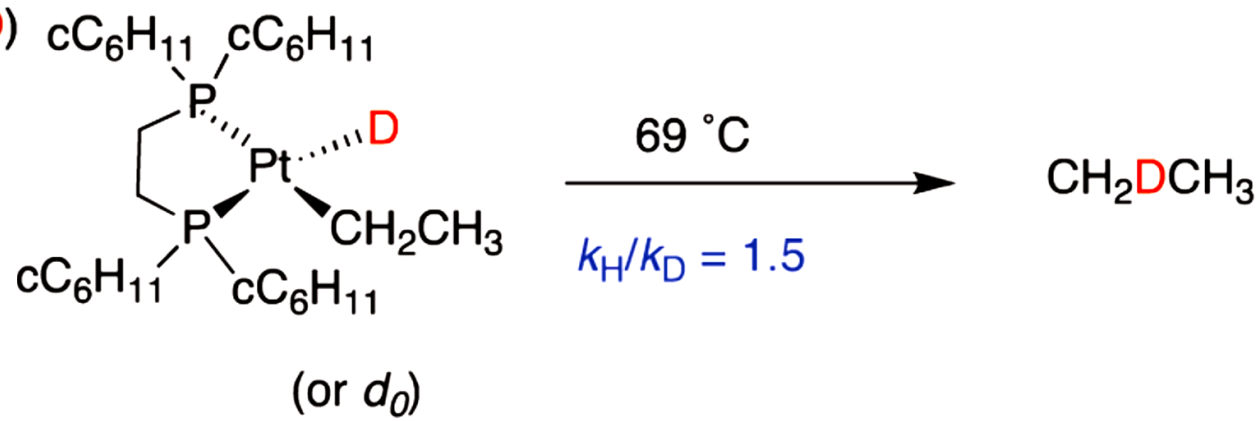
Early Organometallic Studies

- Reductive elimination
  - Study O/A via *microscopic reversibility*
  - Show primary normal KIEs
- Mechanism generally accepted



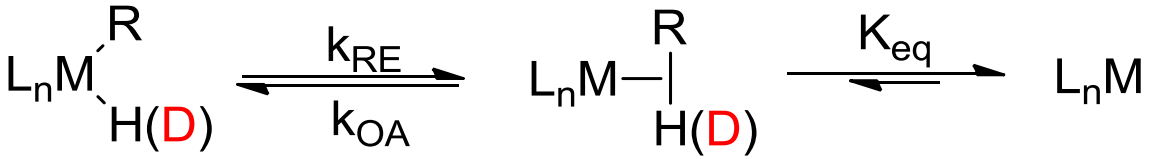


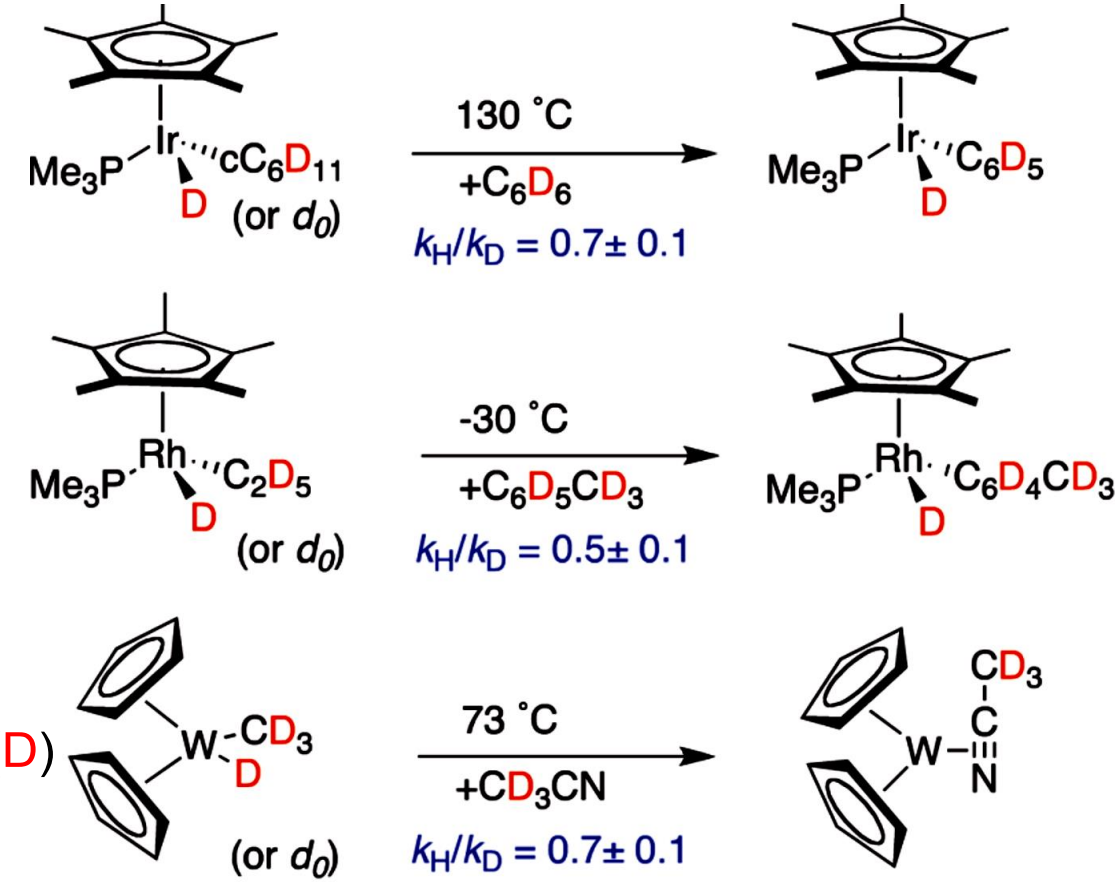




Early Organometallic C-H Activation

- Reductive elimination
  - ***Inverse KIE!***
- Two-step mechanism; three rate constants (k_{RE}, k_{OA}, K_{eq})

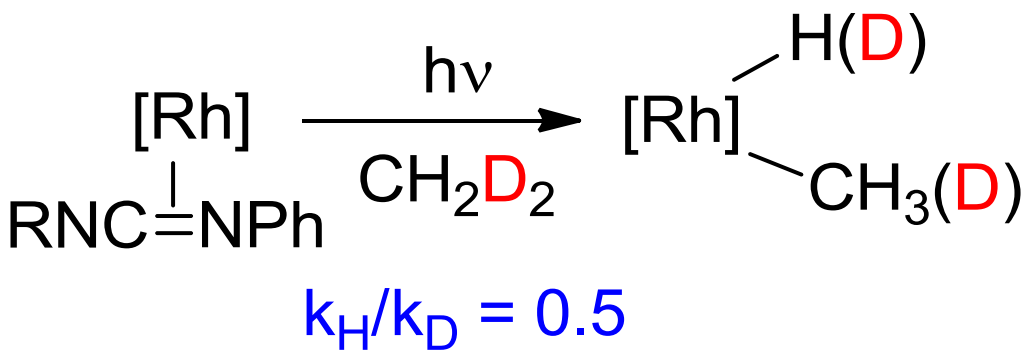


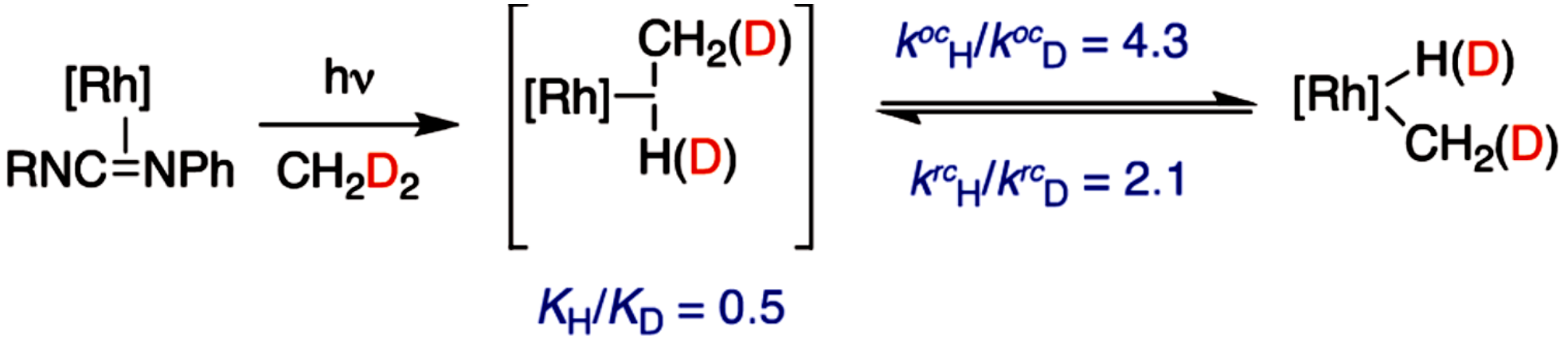


- Assumptions about mechanism convolutes data interpretation

Equilibrium Isotope Effect (EIE)

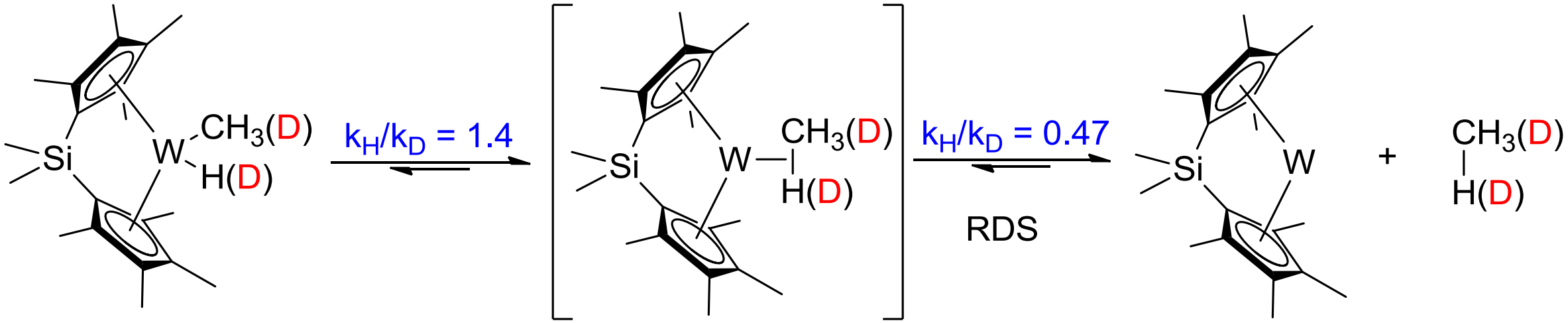
- Apparent inverse KIE
- Actually measuring the EIE





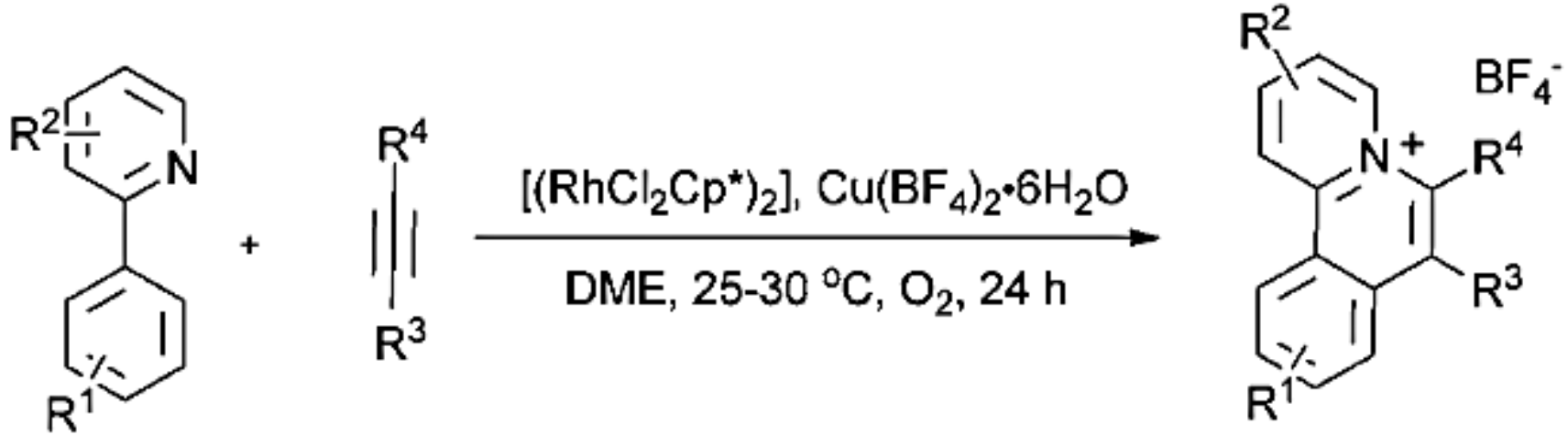
Equilibrium Isotope Effect (EIE)

- Apparent inverse KIE
- Actually measuring a different RDS



An Example

- Organometallic reaction
- Unknown:
  - RDS
  - Mechanism



Luo, C.; Gandeepan, P; Jayakumar, J.; Parthasarathy, K.; Chang, Y.; Cheng, C. *Chem. Eur. J*. **2013**, *19*, 14181–14186.

An Example

- Organometallic rea
- Unknown:
  - RDS
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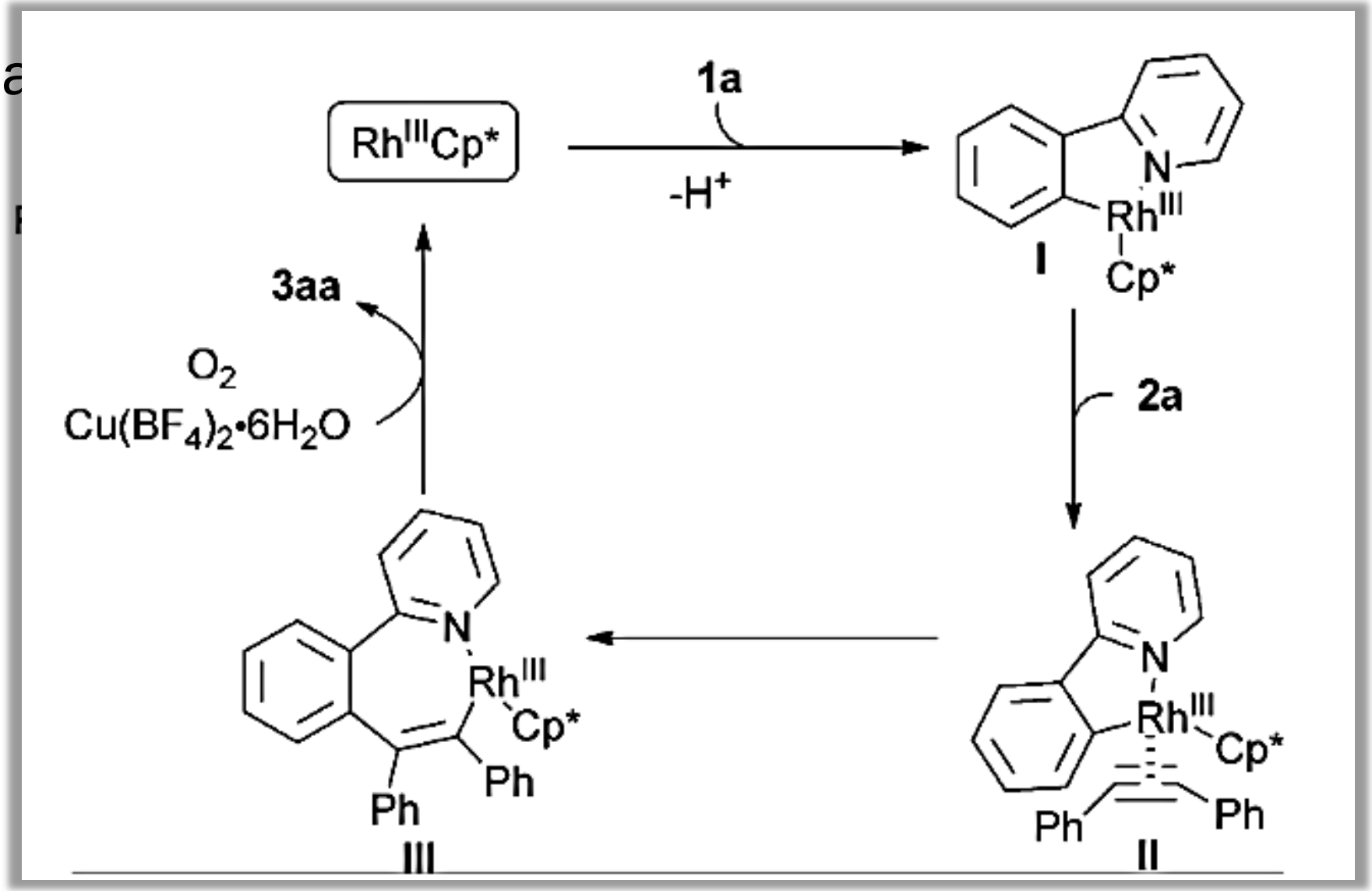

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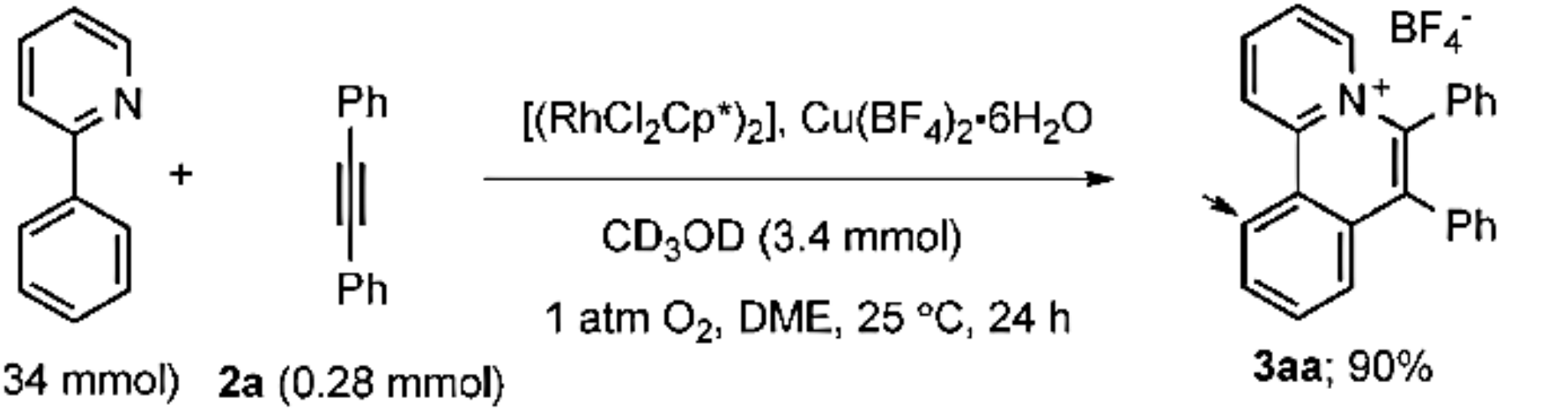
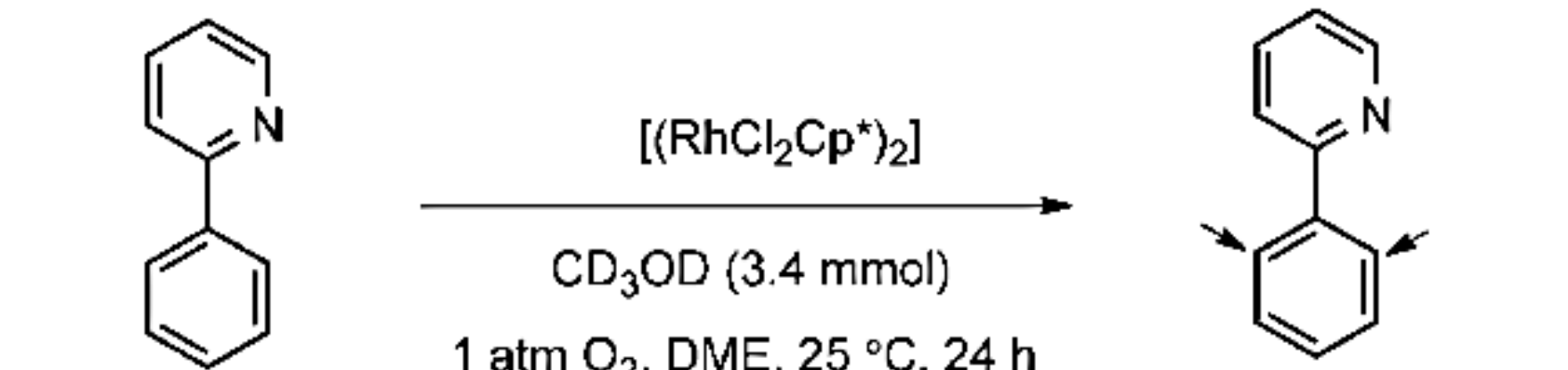


1a (0.34 mmol) **2a** (0.28 mmol)

3aa; 90%

No deuterium/hydrogen exchange



1a (0.34 mmol)

No deuterium/hydrogen exchange

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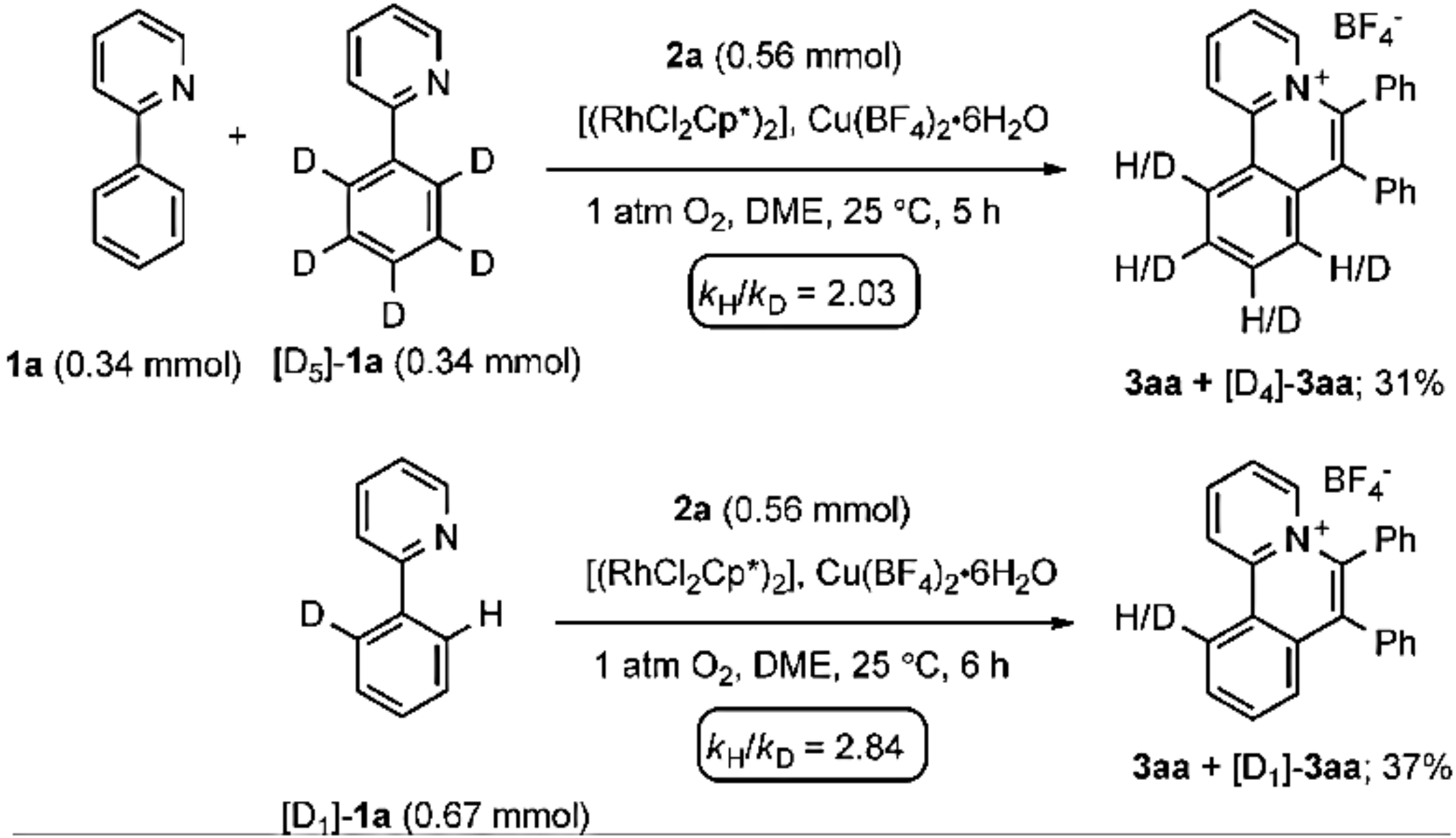
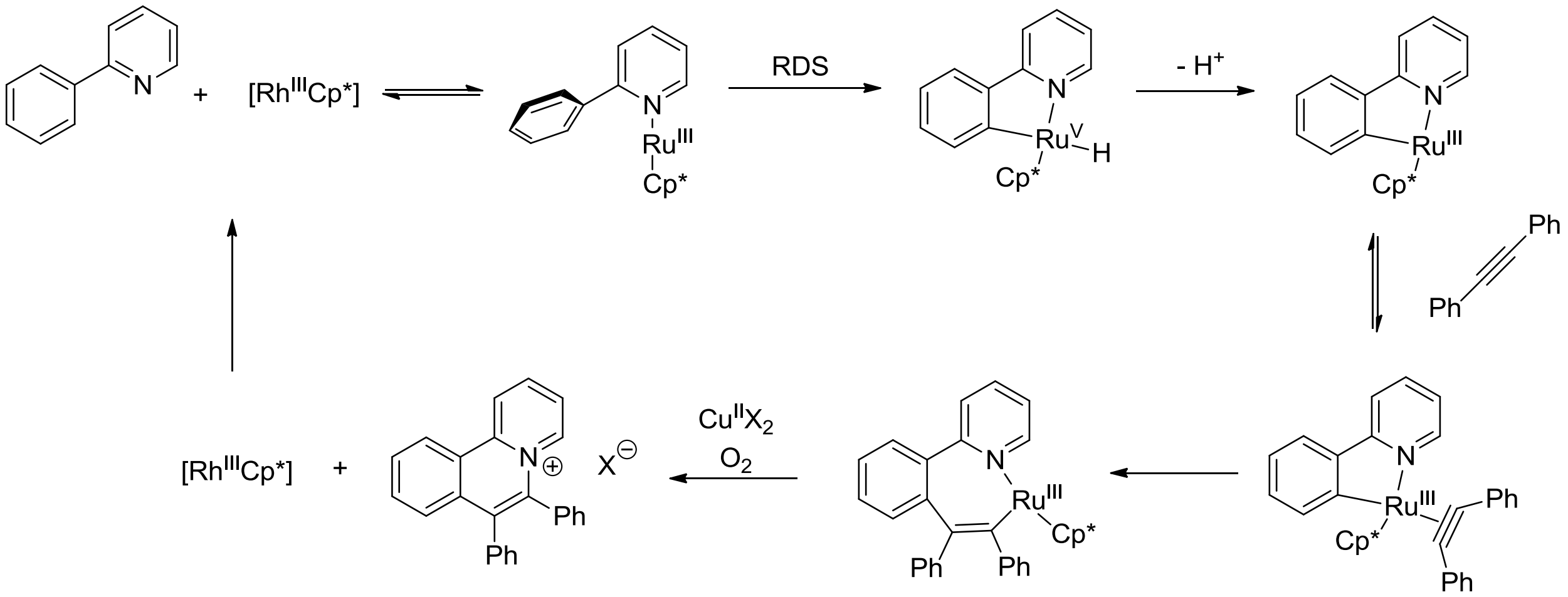


Luo, C.; Gandeepan, P; Jayakumar, J.; Parthasarathy, K.; Chang, Y.; Cheng, C. *Chem. Eur. J*. **2013**, *19*, 14181–14186.

Refined Mechanism



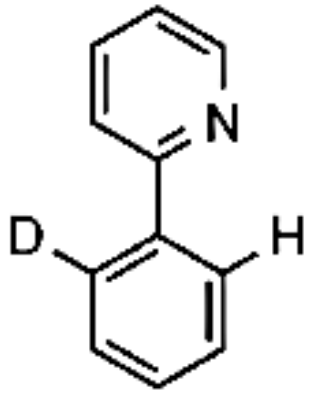
Luo, C.; Gandeepan, P; Jayakumar, J.; Parthasarathy, K.; Chang, Y.; Cheng, C. *Chem. Eur. J*. **2013**, *19*, 14181–14186.

Summary et Conclusions

- KIE is a powerful tool for understanding intimate reaction mechanisms – especially orgaonmetallic
- Caveats
  - Poorly assumed models can lead to ambiguous or contradictory interpretations
  - KIEs are influenced by sterics of D/H and quantum tunneling (if applicable)
  - Small KIEs are often difficult to interpret
- KIE is best used in conjunction with other “classic” mechanistic studies
- Heavier atoms (^{18}O, ^{15}N, ^{13}C, etc.) can be used, however much more difficult to analytically observe KIEs
- Deuterium provides an easy, cheap, NMR-active, MS-“active” label that can get extra information about a reaction (where the D ends up)

$$\frac{k_H}{k_D} = \left(\frac{s_H^{\ddagger} s_D}{s_D^{\ddagger} s_H}\right) \left(\frac{M_H^{\ddagger} M_D}{M_D^{\ddagger} M_H}\right)^{3/2} \left(\frac{I_{AH}^{\ddagger} I_{BH}^{\ddagger} I_{CH}^{\ddagger}}{I_{AD}^{\ddagger} I_{BD}^{\ddagger} I_{CD}^{\ddagger}} \frac{I_{AD} I_{BD} I_{CD}}{I_{AH} I_{BH} I_{CH}}\right)^{1/2}$$

$$\times \left(\frac{\prod_{i=1}^{3N^{\ddagger}-7} \frac{1-e^{-u_{iD}^{\ddagger}}}{1-e^{-u_{iH}^{\ddagger}}}}{\prod_{i=1}^{3N-6} \frac{1-e^{-u_{iH}}}{1-e^{-u_{iD}}}}\right) e^{-1/2\left(\sum_{i=1}^{3N^{\ddagger}-7} (u_{iH}^{\ddagger} - u_{iD}^{\ddagger}) - \sum_{i=1}^{3N-6} (u_{iH} - u_{iD})\right)}$$



2a (0.56 mmol)

$[(RhCl_2Cp^*)_2]$, $Cu(BF_4)_2$•6

1 atm O_2, DME, 25 °C, 6

$k_H/k_D = 2.84$

.67 mmol)

Questions?