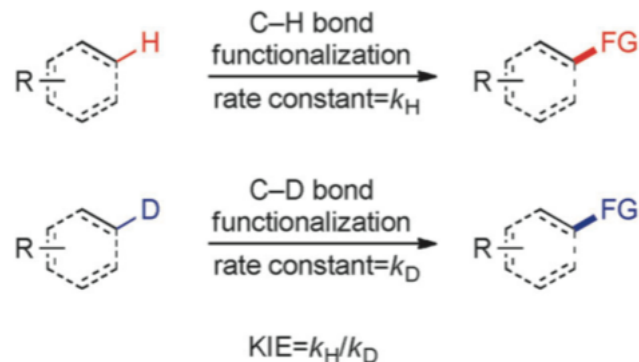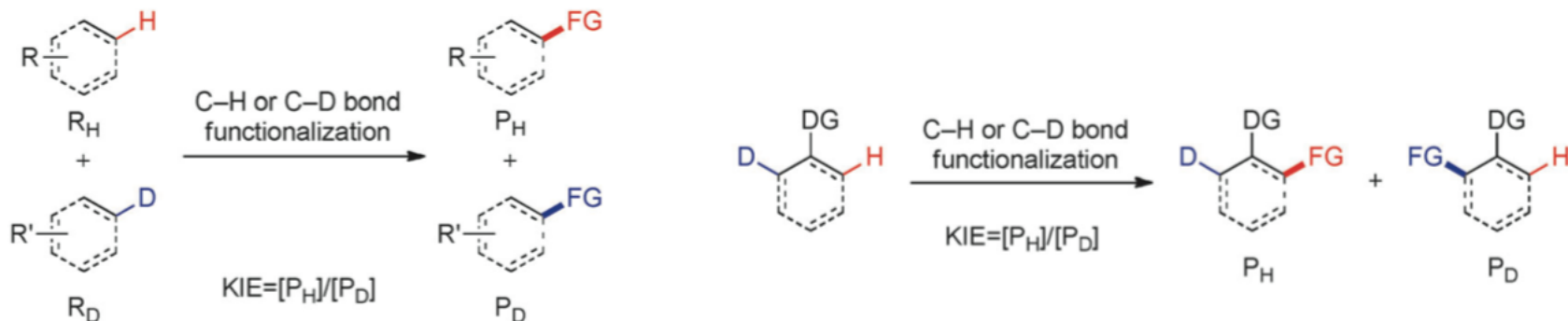# Competitive Kinetic Isotope Effects

Absolute Rates:

- measure rate of H vs. D in separate flasks
- observation of primary KIE is unambiguous evidence for rate-determining C-H cleavage
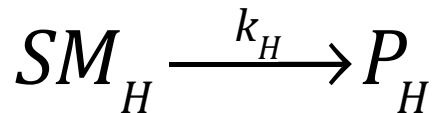- subject to relatively large experimental errors

Intermolecular Competition: measure in same flask using two isotopomeric substrates

Intramolecular Competition: measure in same flask using one substrate that can choose between two isotopes

The methods are more accurate but the results must be interpreted cautiously.

References: Hartwig *ACIE* **2012** *51* 3066; Sierra *Chem. Rev.* **2011**, *4857*; Singleton *JACS* 1995 *117* 9357, *JACS* **1999** *121* 9455; Saunders Reaction Rates of Isotopic Molecules Wiley, **1981**

Intermolecular Competition

$$SM_H \xrightarrow{\ k_H\ } P_H$$
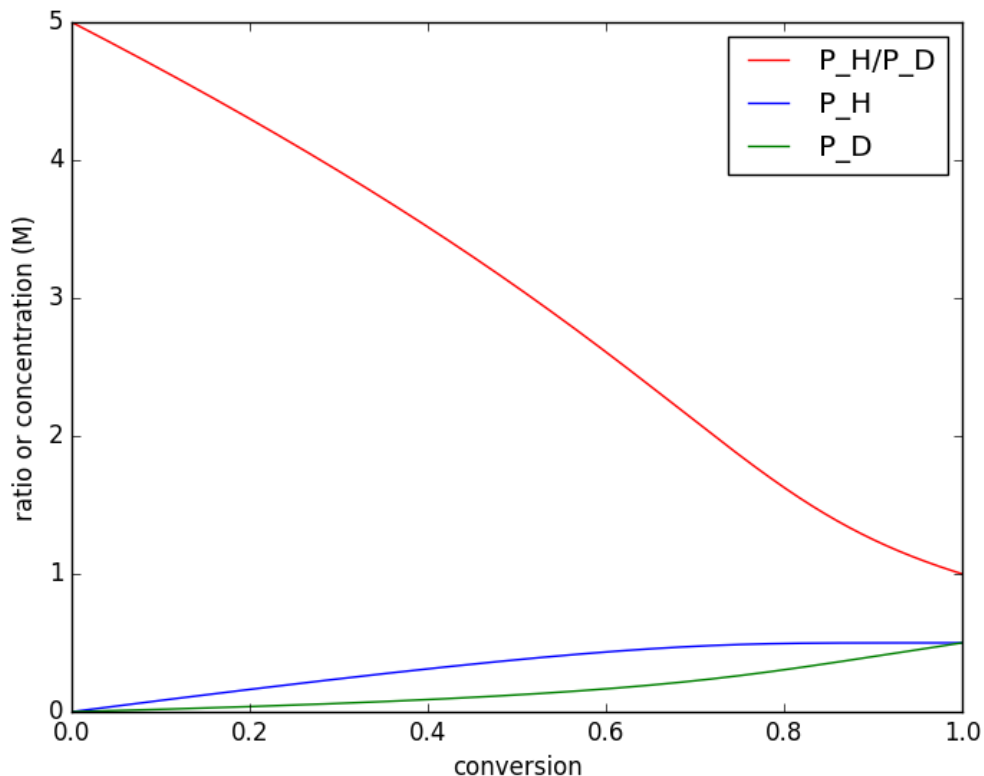
$$SM_D \xrightarrow{\ k_D\ } P_D$$

At *low conversions*, the ratio of <u>product</u> isotopomers will reflect the KIE.
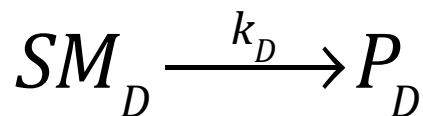
At *high conversions*, the product ratio will equal the starting material distribution.

Simulation for k_H = 0.05 s^{-1} and k_D = 0.01 s^{-1} (KIE = 5.0):

ratio or concentration (M) — vertical axis (0 to 5)

Legend:
- P_H/P_D
- P_H
- P_D

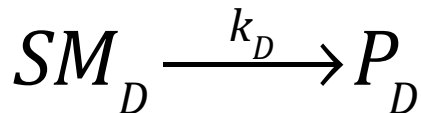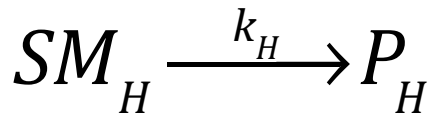**conversion** — horizontal axis (0.0 to 1.0)

The blue and green lines show the product concentrations over the course of the reaction.
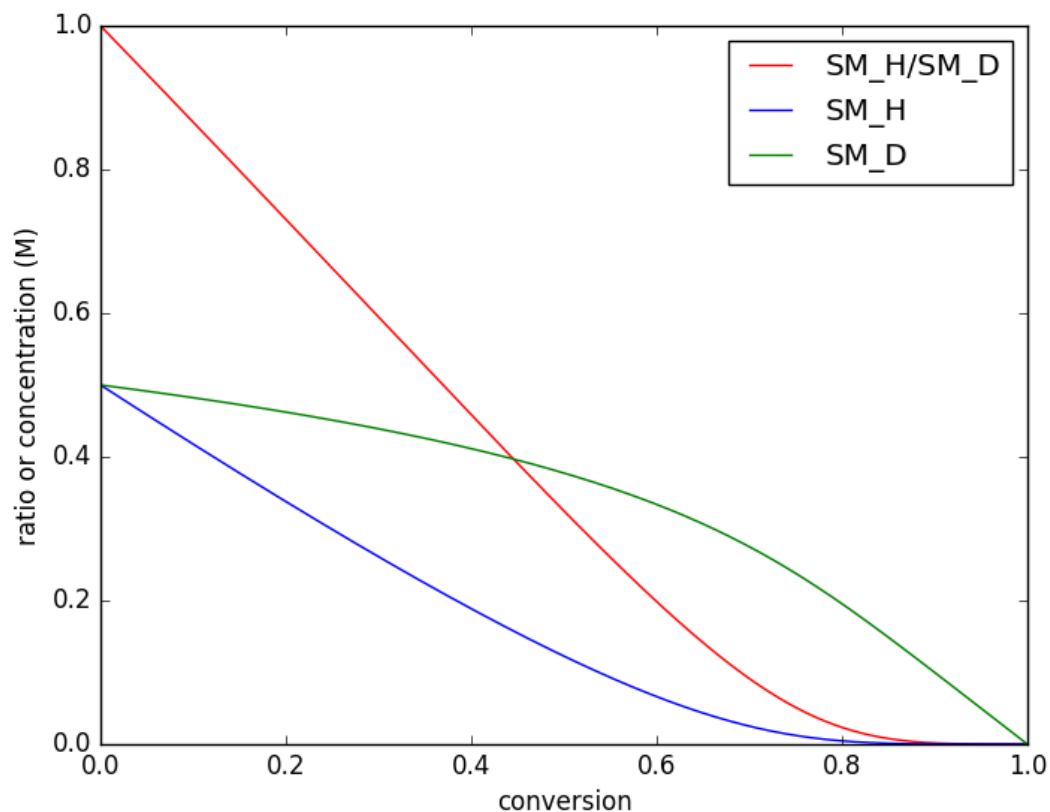
The red line shows the product isotopomer ratio.

This uses a first-order model, but the conclusions do not change with other models.

Intermolecular Competition

$$SM_H \xrightarrow{k_H} P_H$$

$$SM_D \xrightarrow{k_D} P_D$$

At **high conversions**, the starting material will become enriched in the slower reacting isotopomer.

The same simulation is shown below. As conversion approaches 1, the starting material ratio approaches infinity!


The blue and green lines show the starting material concentrations over the course of the reaction.

The red line shows the starting material isotopomer ratio.

The starting material and product situations are **not** symmetric, just as it is in kinetic resolutions. This is because product ratio is constrained to the initial ratio of the starting materials at the end of the reaciton.

Intermolecular Competition

$$SM_H \xrightarrow{\ k_H\ } P_H$$

$$SM_D \xrightarrow{\ k_D\ } P_D$$
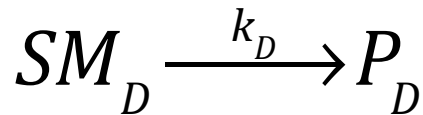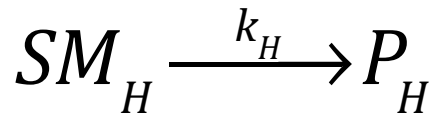
The KIE can be deduced from (see Saunders for derivation):

$$\frac{R}{R_0} = \left(1 - F_1\right)^{\left(\frac{k_D}{k_H} - 1\right)}$$

R and R_0: starting material ratios $[SM_D]/[SM_H]$ at the end and beginning of the reaction, respectively.

F_1: $[SM_H]/[SM_H]_0$ such that $1-F_1$ is the conversion of the protiated starting material

This equation is often simplified to:

$$KIE = \frac{\ln\left(1 - F\right)}{\ln\left[\left(1 - F\right)R/R_0\right]}$$

That is, the overall conversion $1-F$ is assumed to be equal to $1-F_1$. This is dangerous for H/D isotope experiments where KIEs are large and this can be significantly violated.

Intramolecular Competition

$$P_D \xleftarrow{\;k_D\;} D - SM - H \xrightarrow{\;k_H\;} P_H$$
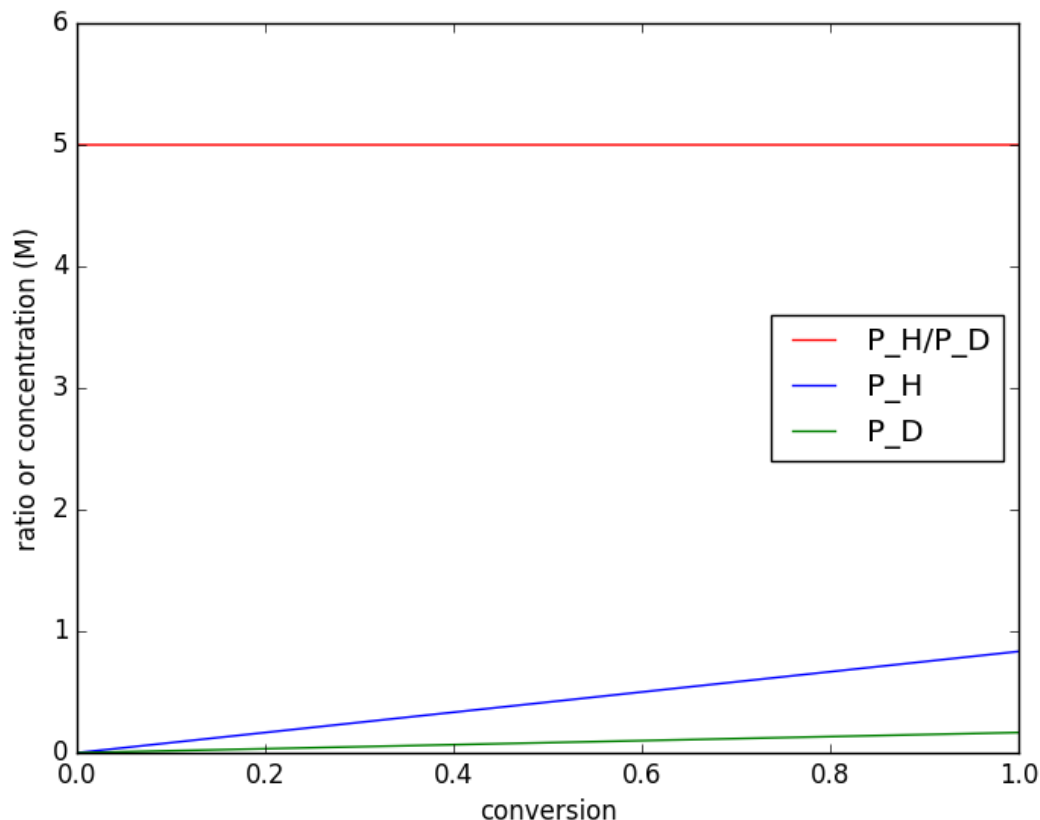
In an **intramolecular** competition experiment, only the <u>product</u> ratio is available. This ratio always reflects the KIE directly.

In a first-order model, this is easy to see mathematically (see left). The integral of an exponential is another exponential, which will result in a term that is the same for the differential equation in P_D. These terms will cancel, leaving k_H/k_D = KIE.
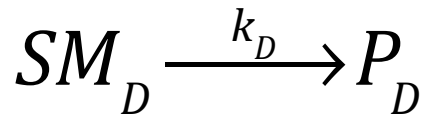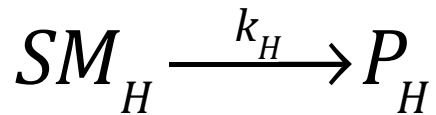
Intuitively, this occurs because the starting material ratio is constrained to 1:1, so every moment is like the start of an intermolecular competition.
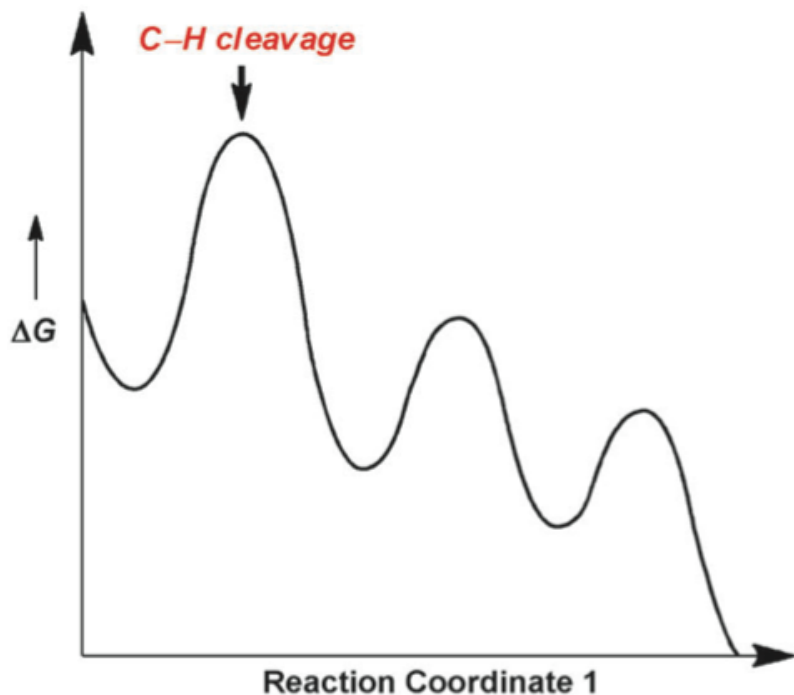
$$[SM] = [SM]_0 \exp\left[-\left(k_H + k_D\right)t\right]$$

$$dP_H/dt = k_H[SM] = k_H[SM]_0 \exp\left[-\left(k_H + k_D\right)t\right]$$

$$dP_H = k_H[SM]_0 \exp\left[-\left(k_H + k_D\right)t\right]dt$$

Scenario 1: The Trivial Case

$$SM_H \xrightarrow{k_H} P_H$$
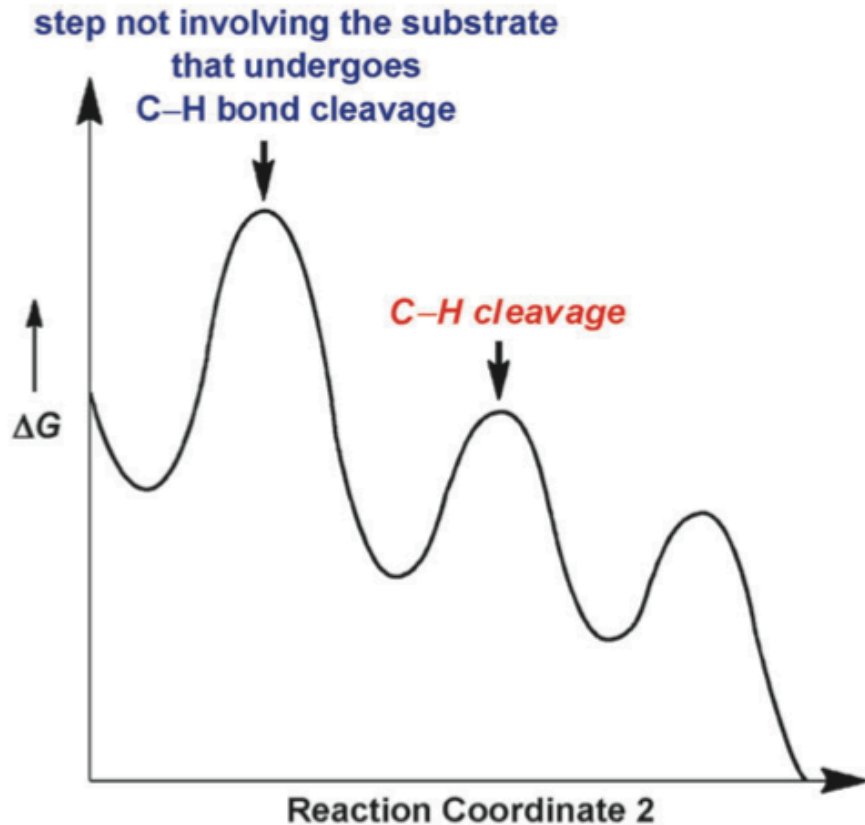
$$SM_D \xrightarrow{k_D} P_D$$

In a one-step reaction, whether the KIE is measured from absolute rates or intermolecular competition, the result will be the same.

If a reaction proceeds via a mechanism in which the first step is rate-determining and involves C-H cleavage, then both experiments will also show a KIE. (Intramolecular competition would also show a KIE.)

However, the situation becomes more complicated if C-H cleavage is post-rate-determining. In general, **competitive KIEs do not have to reflect the KIE of the rds.**
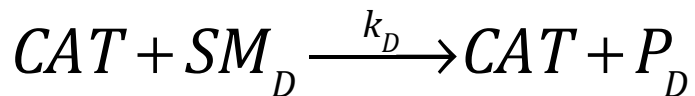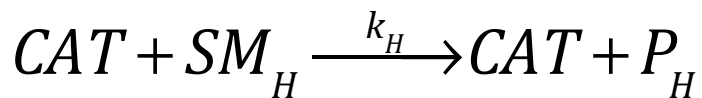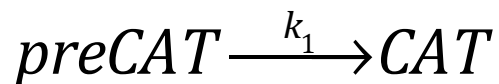
Scenario 2: Rate-Determining Catalyst Activation

step not involving the substrate
that undergoes
C–H bond cleavage

ΔG

C–H cleavage

Reaction Coordinate 2

$$preCAT \xrightarrow{k_1} CAT$$

$$CAT + SM_H \xrightarrow{k_H} CAT + P_H$$
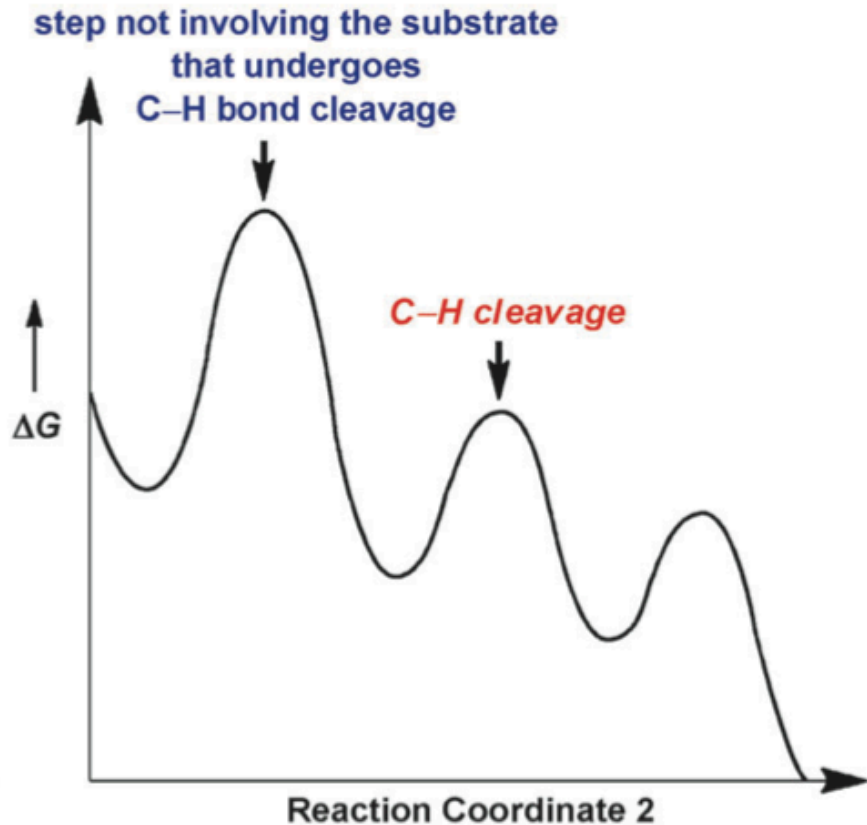
$$CAT + SM_D \xrightarrow{k_D} CAT + P_D$$

For example, consider another trivial example where the rate (or turnover) limiting step involves catalyst activation. This could be a ligand dissociation or reductive elimination from a metal complex.

Absolute rates will just measure the rate of catalyst activation, which is obviously not sensitive to whether the substrate has H or D.

Competition experiments could show a KIE, however! The slow catalyst activation process trickles active catalyst into the reaction. Imagine running the experiment by trickling in active catalyst. Clearly, a competitive KIE would be observed. In this case, the absolute rate measures the rate of the catalyst addition, while the competitive KIE measures the preference of the catalyst for H vs. D.
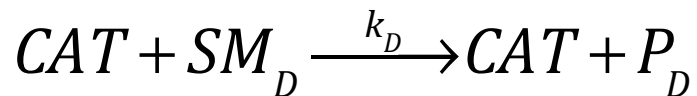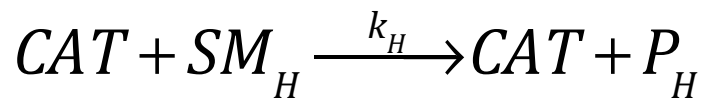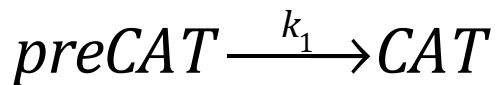
Scenario 2: Rate-Determining Catalyst Activation

step not involving the substrate
that undergoes
C−H bond cleavage

ΔG

C−H cleavage

Reaction Coordinate 2

$$preCAT \xrightarrow{\;k_1\;} CAT$$

$$CAT + SM_H \xrightarrow{\;k_H\;} CAT + P_H$$
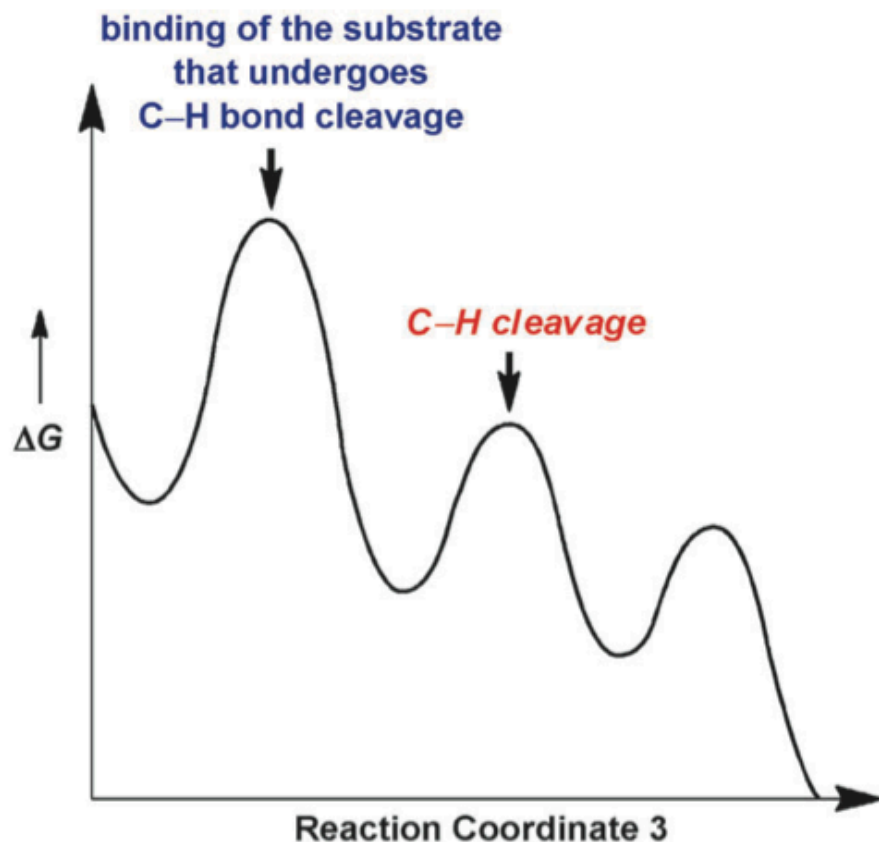
$$CAT + SM_D \xrightarrow{\;k_D\;} CAT + P_D$$

A simulation with $k\_1 = 0.001$, $k\_H = 0.5$, $k\_D = 0.1$, $[preCAT]_0 = 0.05$, $[SM_H]=[SM_D]=0.5$:
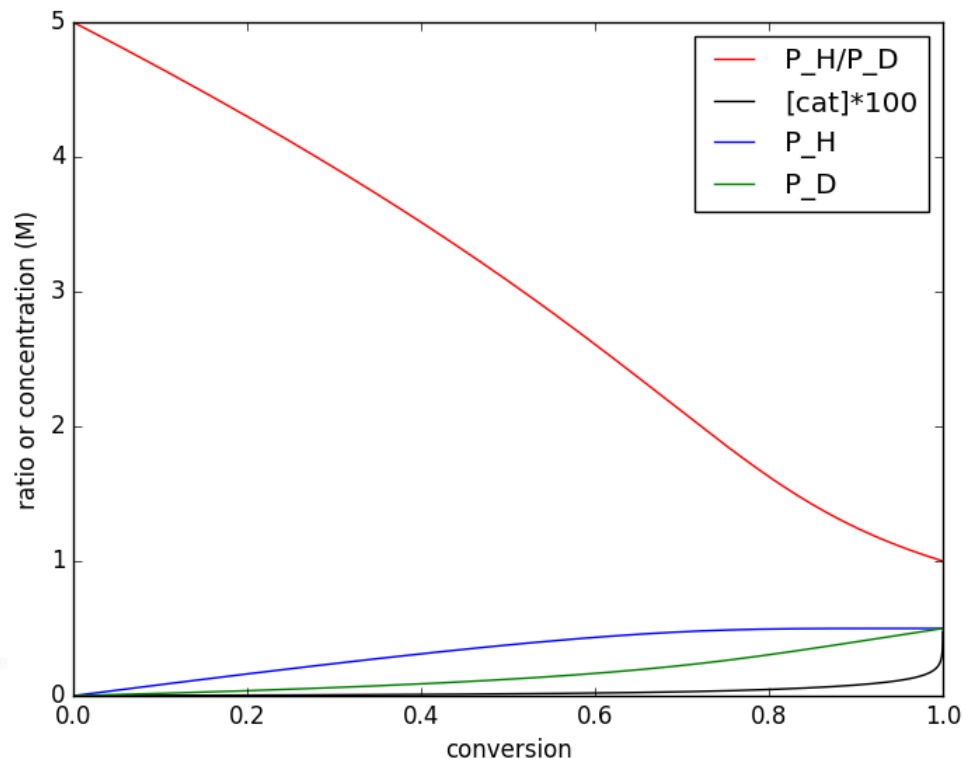
The catalyst concentration (black) is very low for the reaction, yet a post-rate-determining KIE (red) is being observed!

Scenario 3: Rate-Determining Substrate Activation

binding of the substrate
that undergoes
C–H bond cleavage
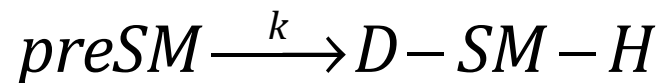
C–H cleavage

ΔG

Reaction Coordinate 3

What if the rate-determining step involves the substrate, but does not involve C-H cleavage? This could be pi-complexation to the catalyst, or perhaps oxidative addition to a C-X bond in the substrate.
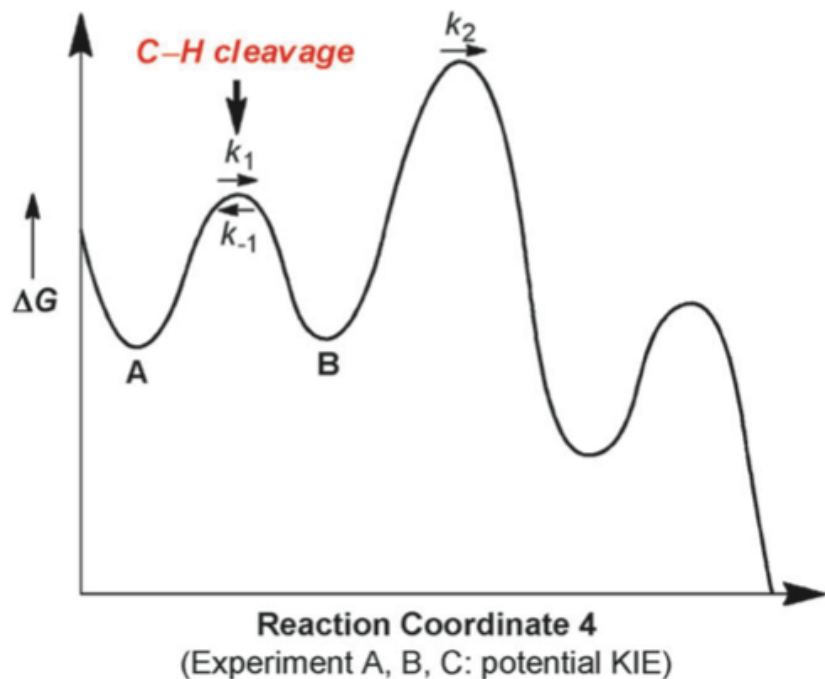
Absolute Rates: No KIE because C-H cleavage is not in the rate law.

Intermolecular Competition: No KIE because substrate activation is also product-determining, which is isotopically insensitive.

Intramolecular Competition: KIE observed! The product determining step in this experiment is now the C-H cleavage step.

$$preSM \xrightarrow{k} D-SM-H$$

$$P_D \xleftarrow{k_D} D-SM-H \xrightarrow{k_H} P_H$$

Scenario 4: Pre-Equilibrium Cleavage

C–H cleavage

k_2

k_1

k_{-1}

ΔG

A

B

Reaction Coordinate 4
(Experiment A, B, C: potential KIE)

What if C-H cleavage occurs *before* the rate-determining step?

Assuming pre-equilibrium kinetics, the rate law in this situation is:

$$v_H = k_2[B_H] = K_H\, k2_H\, [A_H]$$
$$v_D = k_2[B_D] = K_D\, k2_D\, [A_D]$$

Measuring the KIE amounts to measuring

$$(K_H/K_D)\, (k2_H/k2_D)$$

which is the product of the equilibrium isotope effect (EIE) and KIEs.

Regardless of how the KIE is measured, the isotope effect will be much smaller because EIE << KIE. Absolute rates will show the effect because it is in the rate law. Relative rates will show the effect because the reaction is committed to an isotope at the rds.

If both steps 1 and 2 are isotopically sensitive, the two isotope effects will be superimposed.

Scenario 5: Post-Rate-Determining Equilibrium Cleavage
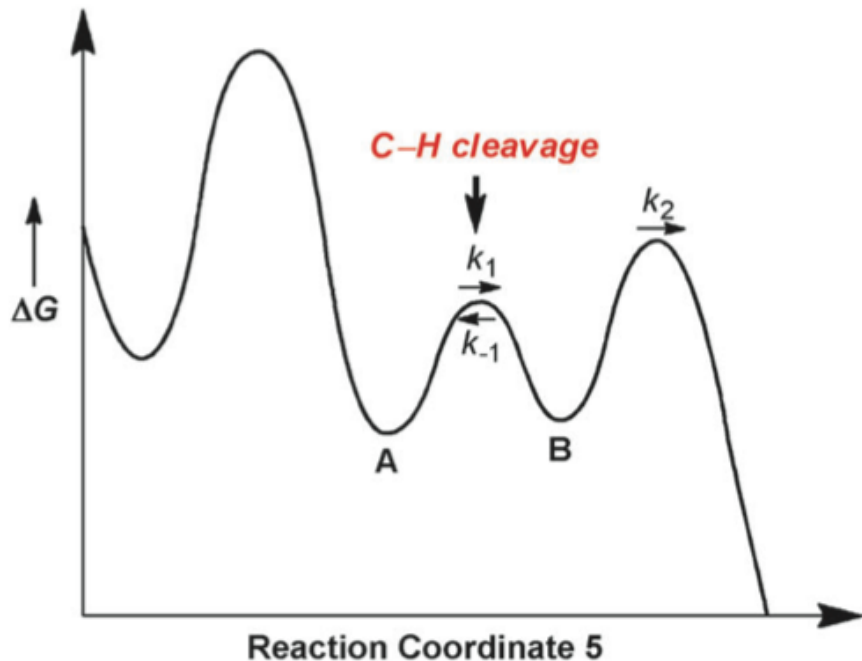
If equilibrium C-H cleavage occurs *after* the rate-determining step, the rate law cannot be affected.
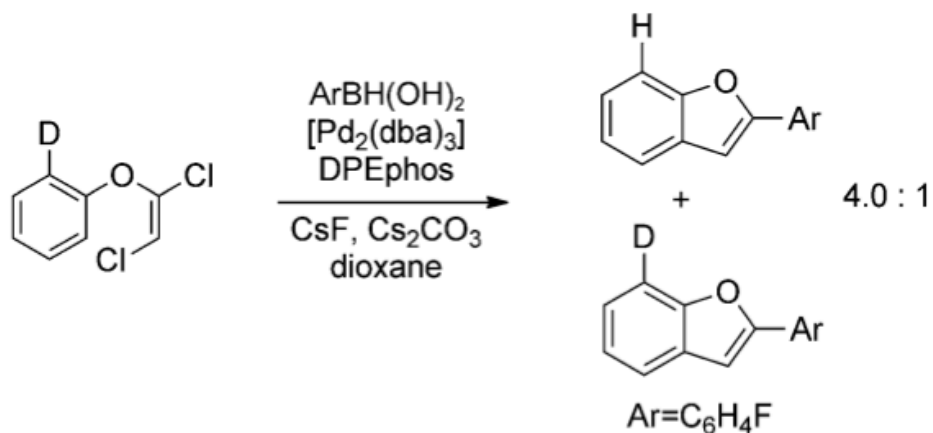
Absolute rates: No KIE.

Competition: EIE.

However, competition experiments can show an EIE because it can perturb the rate of the product-determining step. In this diagram, the product is committed to an isotope in step k2. This rate of this step depends on [B], which is affected by the EIE.
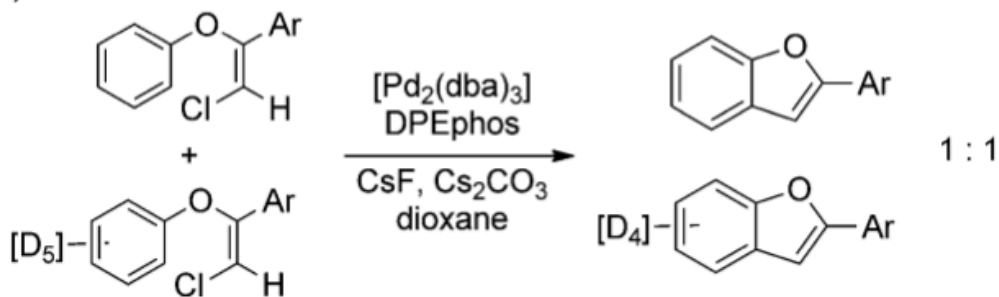
Example 1

a)

ArBH(OH)$_2$
[Pd$_2$(dba)$_3$]
DPEphos
—————————→
CsF, Cs$_2$CO$_3$
dioxane

+   4.0 : 1   Intramolecular KIE: yes

Ar=C$_6$H$_4$F

b)

[Pd$_2$(dba)$_3$]
DPEphos
—————————→
CsF, Cs$_2$CO$_3$
dioxane

1 : 1   Intermolecular KIE: no

This means that C-H cleavage is **not** rate-determining. In fact, oxidative addition to the C-Cl bond is rate-limiting. In experiment a), the substrate is not committed to an isotope at this stage, so an intramolecular KIE can be observed. In experiment b), the substrate *is* committed to an isotope during C-Cl oxidative addition, so an intermolecular KIE cannot be observed. Geary *Eur. JOC* **2010** 5563
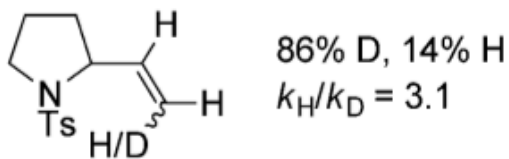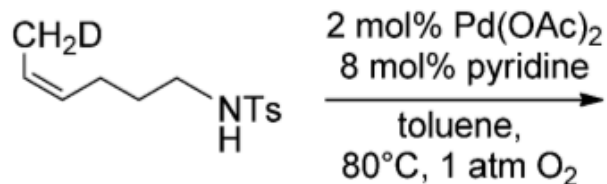
Example 2

a)
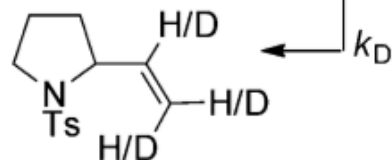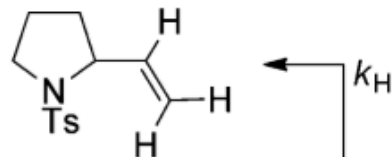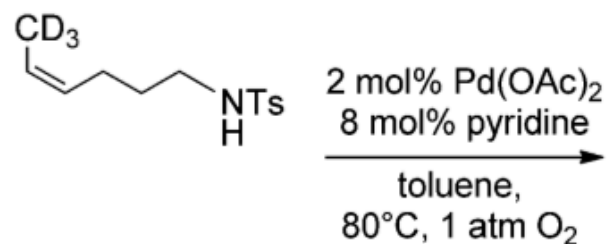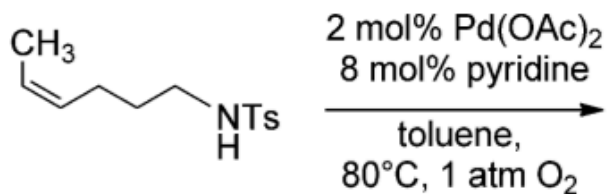
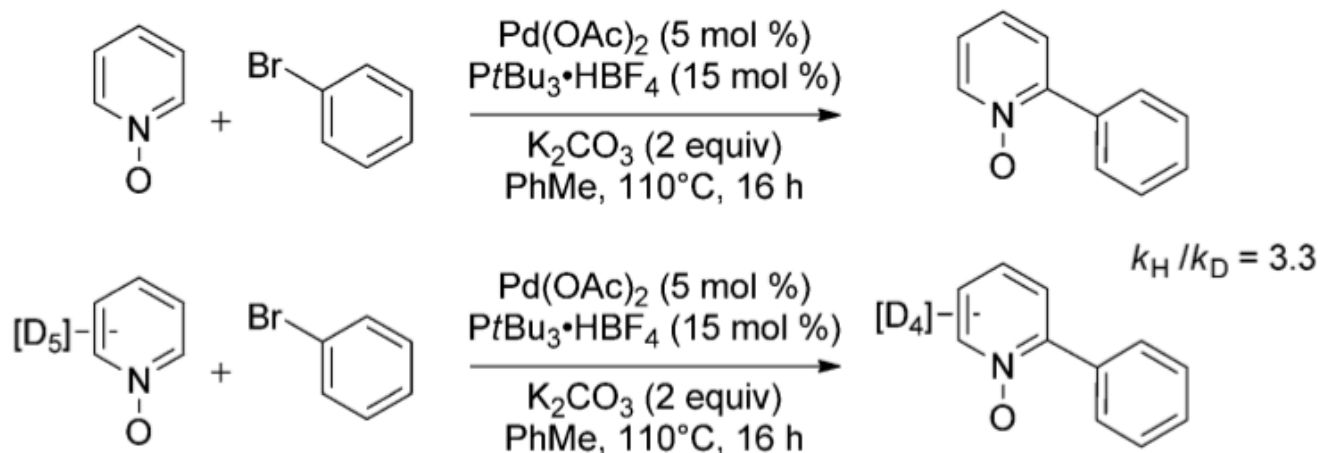$k_H/k_D = 1.2$ Intermolecular KIE: no

b)

86% D, 14% H
$k_H/k_D = 3.1$ Intramolecular KIE: yes

The same arguments apply to this reaction. C-H cleavage cannot be rate-limiting. The observed result in a) could be an EIE or a secondary isotope effect from a different step.

Stahl *JOC* **2011** *76* 1031

Example 3

The observation of an absolute KIE indicates rate-determining C-H cleavage.
Fagnou *JOC* **2010** *75* 8180

In general, the observation of a competitive KIE establishes that there *might* be rate-determining C–H cleavage. Conversely, the lack of a competitive KIE establishes that C–H cleavage *cannot* be rate-determining. In the former case, absolute rate studies should be performed. That is, if one wishes to establish whether C–H cleavage is rate-determining, then one must measure the actual rate of the reaction (with both isotopes).

None of this means that competitive KIEs are useless, however. They can still provide a wealth of other information (see Chem. Rev.).