Lecture 22: Asymmetric Catalysis

Announcements

- Problem Set 6 is posted on the course website. Due Fri, 12/8 by 5pm to Mary's office (209 LDL)
- Extra practice problems also posted on course website (just 2).
- Online course evaluations: Fri, 12/1 – Sun, 12/10: http://www.udel.edu/course-evals/
- Seminars:
    - Biochem Faculty Candidate: Glen Liszczak, Fri, 10am, 219 BRL, ***Seq-ing answers: Decoding epigentic mechanisms with protein chemistry***
    - Prof. Chris Jeffrey, Fri, 4pm, 219 BRL, ***Exploring natural products variation leads to chemical discoveries***

Today

- Asymmetric Catalysis
    - Design principles
    - Kinetic considerations
- Other mech experiments

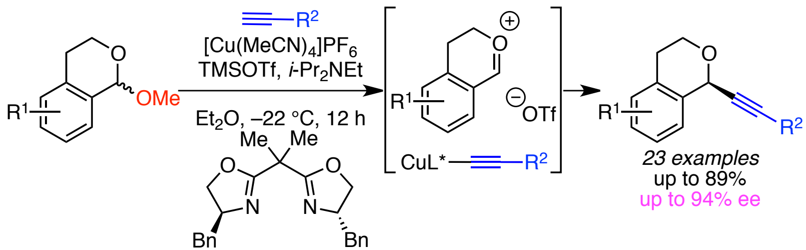
Catalyst/Ligand Design

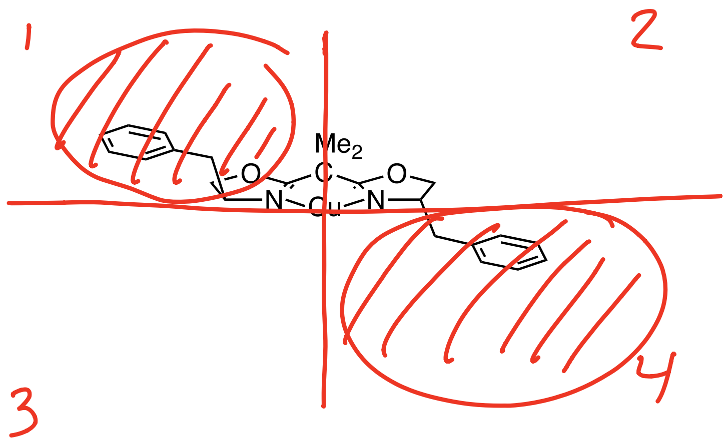
$L^* - M$ or cat^*

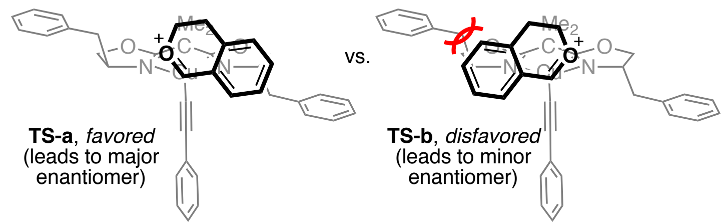
Design Principles:

1) Symmetry
   → Often C_2

Quadrant Formalism







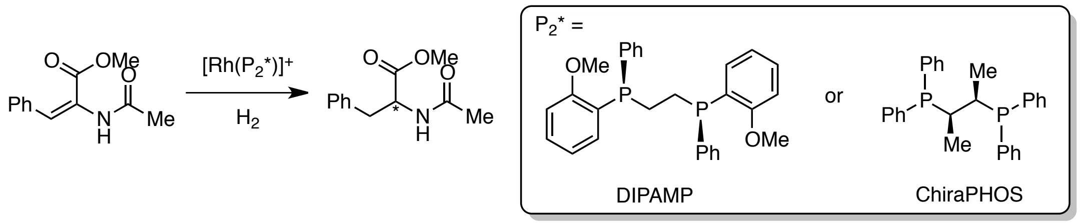
TS-a, *favored* (leads to major enantiomer)

TS-b, *disfavored* (leads to minor enantiomer)

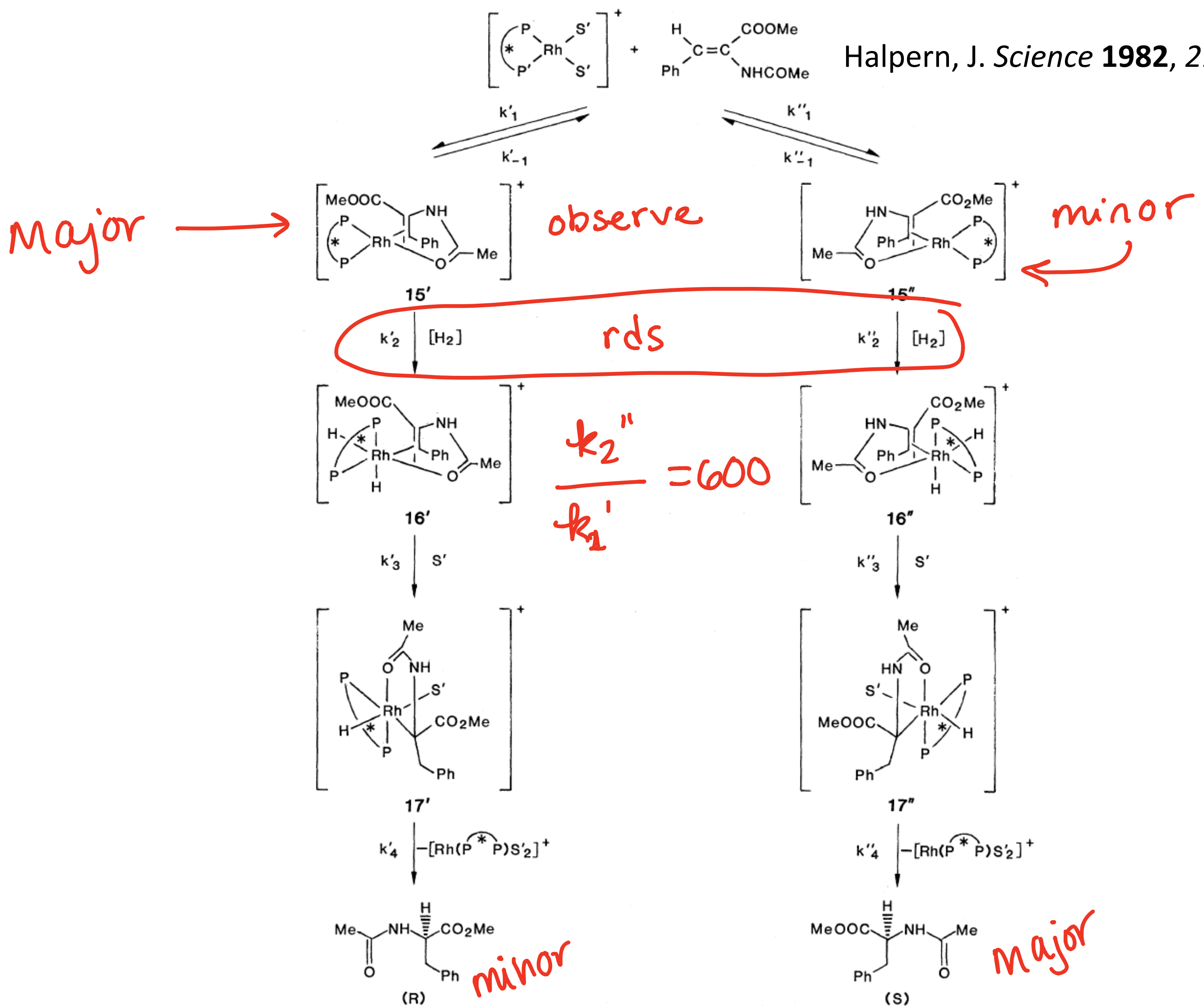
Maity, Srinivas, Watson. *JACS* 2011, 17142

2nd Design Principle: It's hard to depict TS's... so people often think about intermediates. This can be completely wrong.

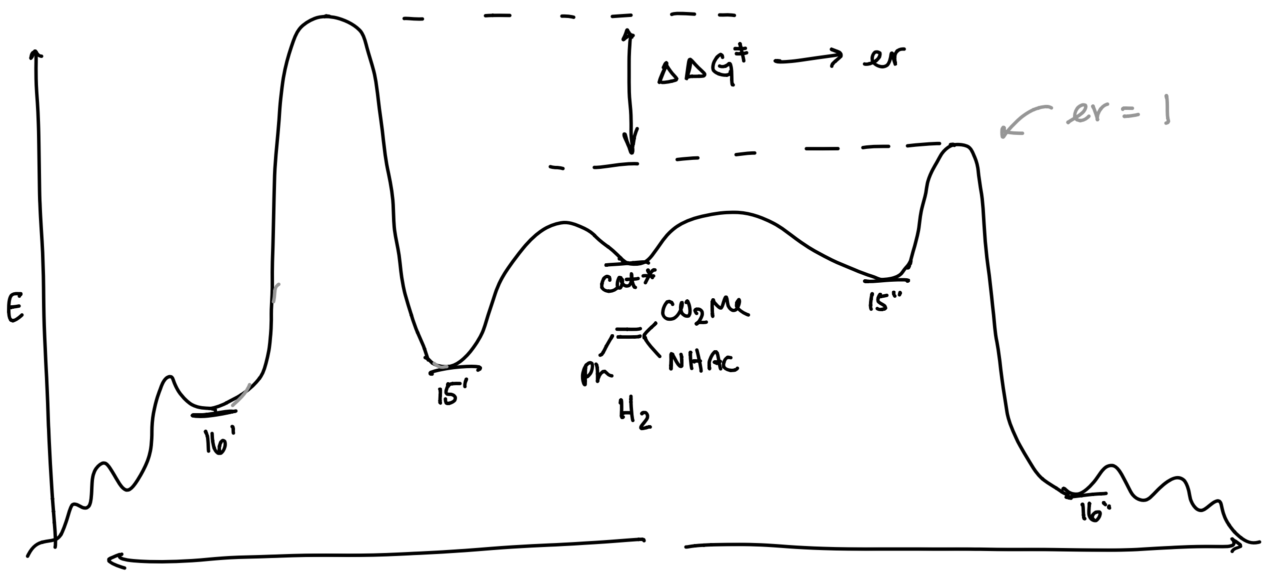
Asymmetric Hydrogenation & Curtin-Hammett Situations



Halpern, J. *Science* **1982**, *217*, 401



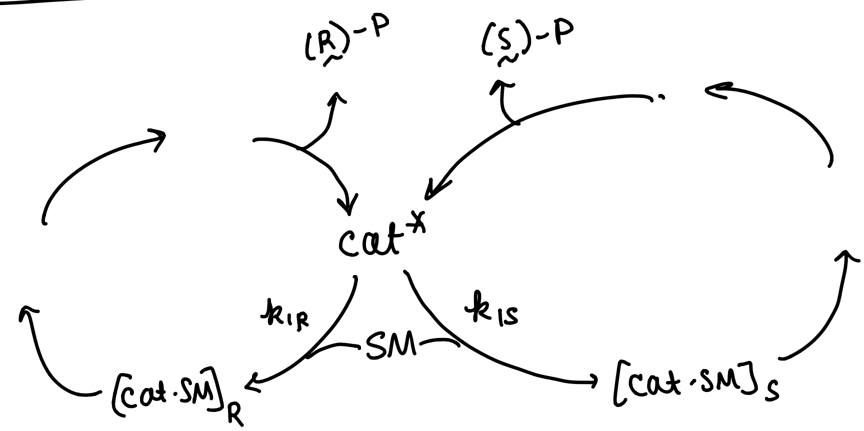
Halpern, J. *Science* **1982**, *217*, 401



Curtin-Hammett Situation:

- Rapid equilibration of intermediates <u>before</u> rds/enantiodetermig step.

<u>Kinetic Considerations</u>



$$k_{1R} \neq k_{1S}$$

$$rate = \frac{d[(R)\text{-}P]}{dt} + \frac{d[(S)\text{-}P]}{dt}$$

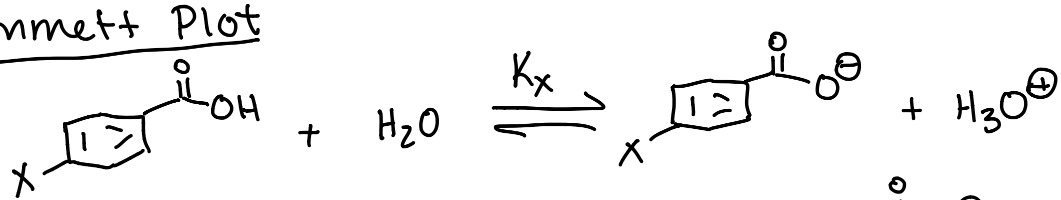
$$rate_R = \frac{\dfrac{k_{1R}\, k_{2R}\, k_{3R} \cdots [cat^*]_{total} [SM][\cdots]}{k_{-1R} \cdots}}{1 + \text{"}[cat \cdot SM]_R\text{"} + \text{"}[cat \cdot SM]_S\text{"}}$$

Other Mechanistic Tools

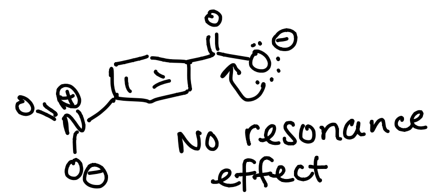
Linear Free Energy Relationships (LFER's)

- probes substituent effects on kinetics or thermodynamics of a reaction

Hammett Plot



K_X vs. K_H



$$\sigma_p = \log\left(\frac{K_X}{K_H}\right) = pKa_H - pKa_X$$

↑ measure of substituent's ability to donate/withdraw e- density by induction

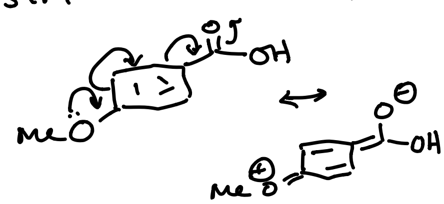
$\sigma_p > 0 \Rightarrow$ X is better at stabilizing ⊖ than H

X = inductively electron-withdrawing

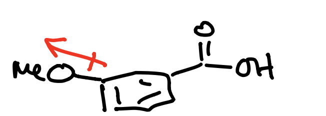
$\sigma_p < 0 \Rightarrow$ X = inductively electron-donating

Table 8.2 for common substituents (A & D)

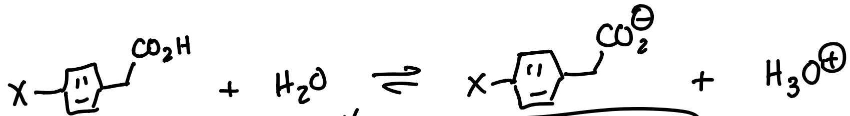
Position matters:



X	σ_p	σ_m
H_3CO–	−0.27	+0.10
HO–	−0.38	+0.13



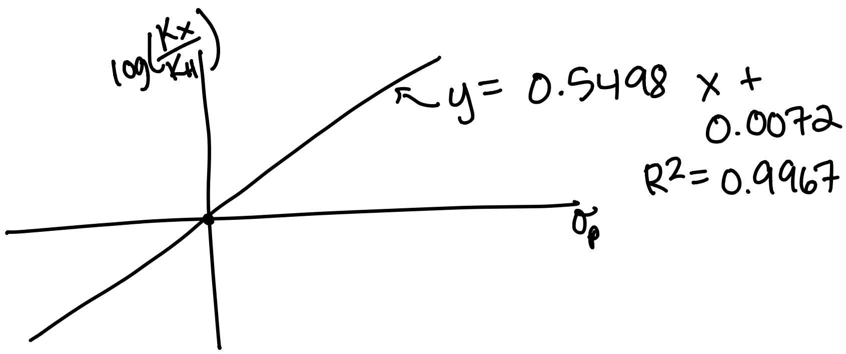
Why is this useful?



X	σ_p	$\frac{K_{sub}}{K_{unsub}}$	log( )
Me	−0.14	0.87	−0.060
OMe	−0.27	0.89	−0.051
H	0	1	0
Cl	0.24	1.32	0.1257
NO_2	0.81	2.89	0.4609

J Chem Soc 1938, 357

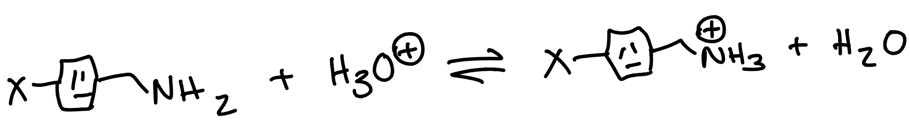
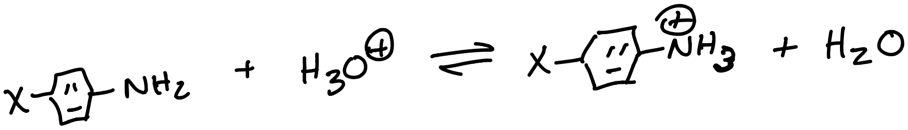
Hammet Plot:



Slope = +0.55 = ρ

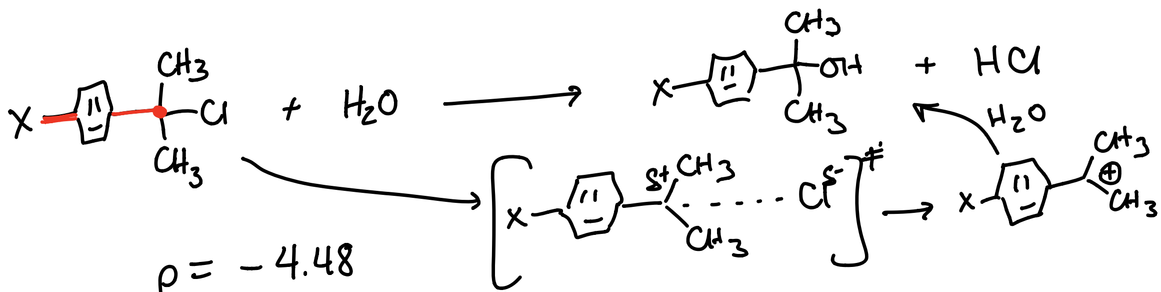
⊕ρ ⇒ Build-up of ⊖ charge

⊖ρ ⇒ Build-up of ⊕ charge

	ρ
	2.26
	−1.05
	−3.19

Also applies to TS's !! ◡̈

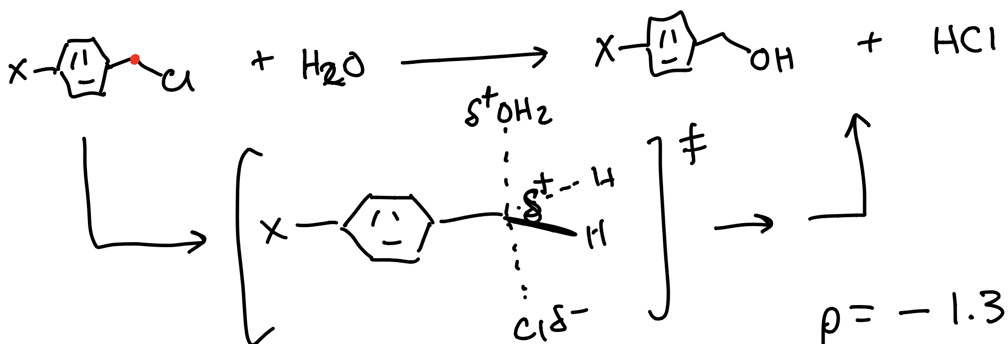
→ Measure $\frac{k_X}{k_H}$. Plot σ vs. $\log\left(\frac{k_X}{k_H}\right)$



$\rho = -4.48$

↑ build-up of ⊕ in TS

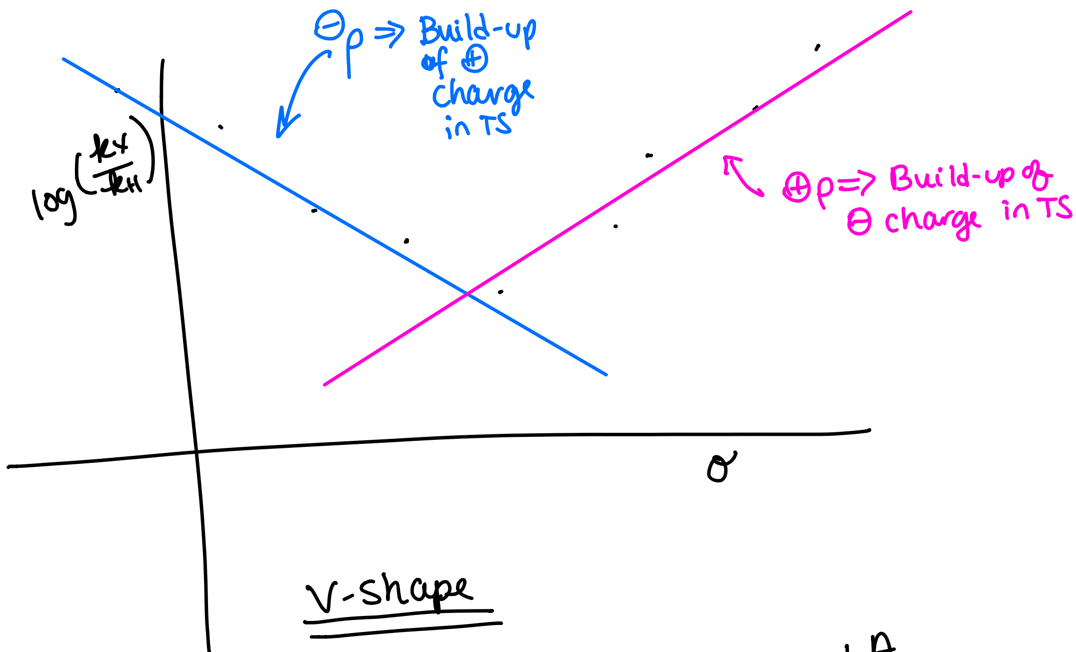
prototypical for S_N1.



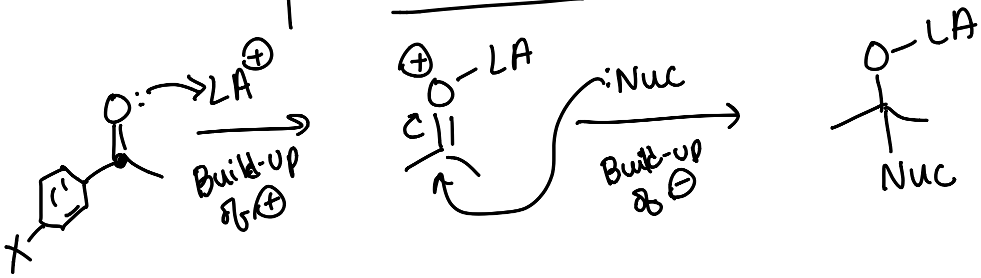
$\rho = -1.31$

prototypical for S_N2.

Other LFER's ⇒ Steric ⇒ Charton values


⊖ρ ⇒ Build-up of ⊕ charge in TS
⊕ρ ⇒ Build-up of ⊖ charge in TS
log(kX/kH)
σ

V-shape


LA⊕
Build-up of ⊕
:Nuc
O–LA
Build-up of ⊖
Nuc
X