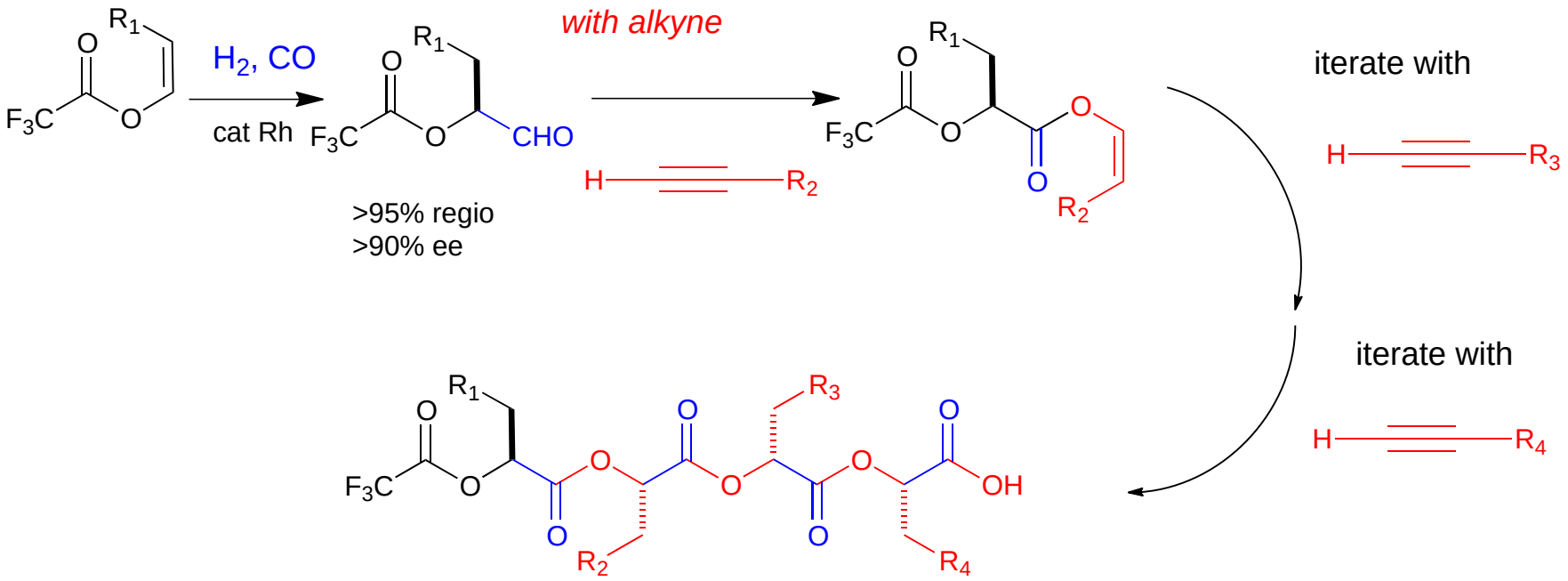
Toward Chiral Condensation Polymers

Asymmetric Hydroformylation

1. Oxidize -CHO to -CO_2H
2. Ru-catalyzed -CO_2H coupling with alkyne



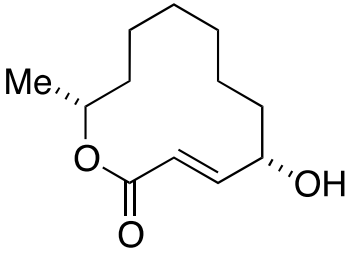
R_1 = H
R_2 = hexyl
R_3 = $CH_2CH_2CH_2Ph$
R_4 = $CH_2CH_2CH_2OMe$

>90 of single diastereomer
>50% yield based on alkyne
Pinnick oxidation

- ✓ >98% atom economical (no coupling agents)
- ✓ Sequence-specific
- ✓ All stereocenters introduced catalytically
- ✓ AHF proceeds with >95% regioselectivity and >90% ee

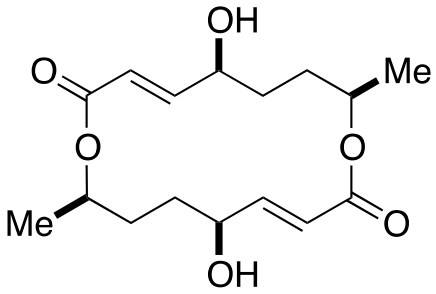
Burke AHF Examples

AHF/ Intramolecular Wittig Olefination



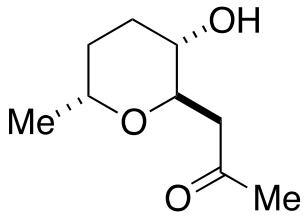
(+)-Patulolide C

AHF/ Intermolecular Wittig Olefination

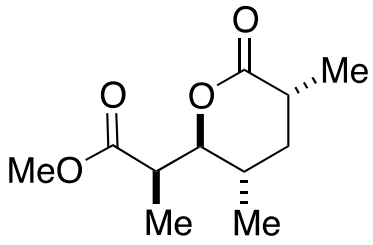


(-)-Pyrenophorol

AHF/ Crotylation



(+)-Decarestrictine L



(+)-Prelog Djerassi Lactone

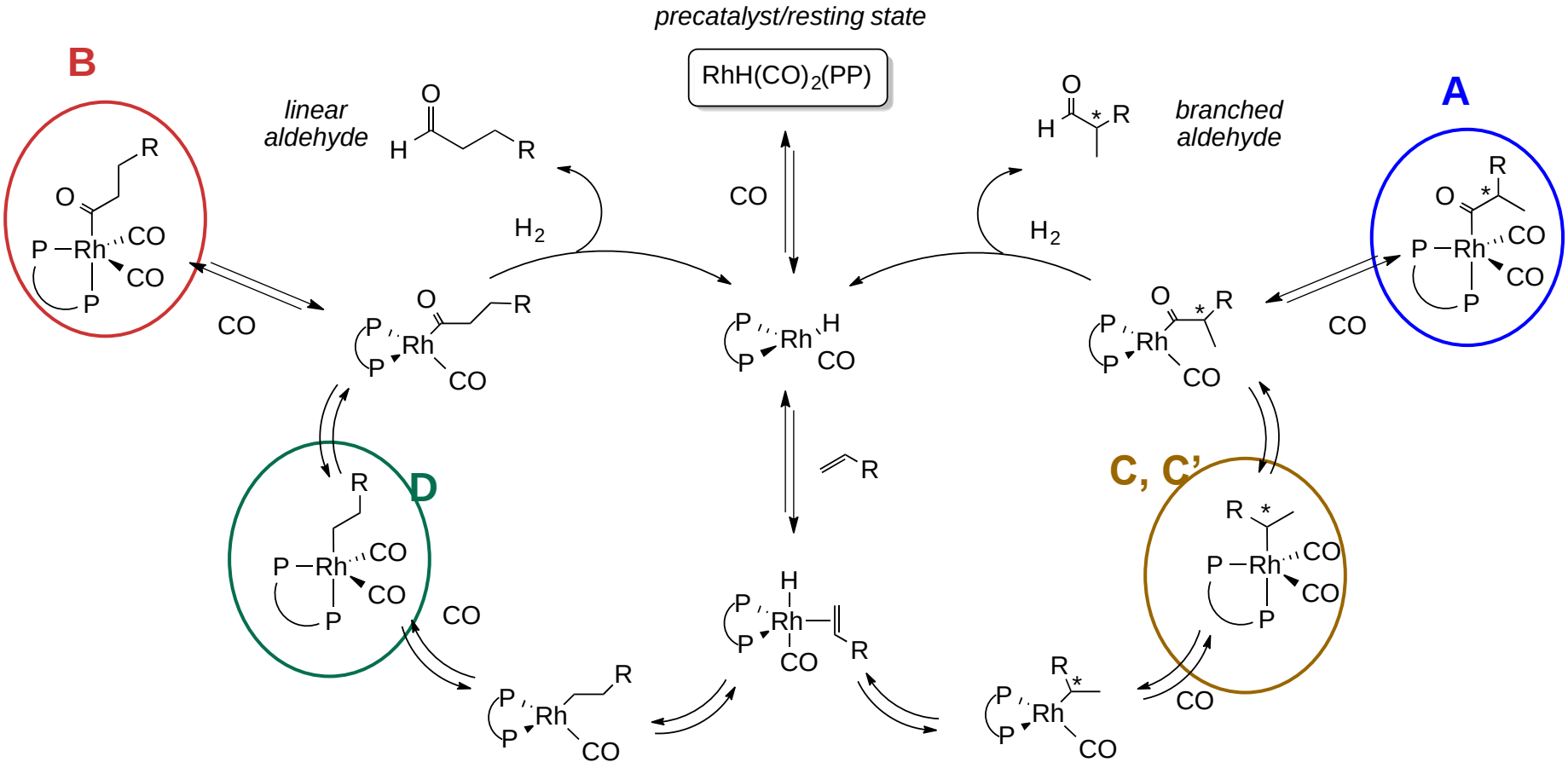
	AHF Tandems		Previous Syntheses	
Target	Steps	Overall % Yield	Steps	Overall % Yield
(+)-Patulolide C	3	49	9-19	2-33
(-)-Pyrenophorol	5	32	11-16	2-11
(+)-Decarestrictine L	4	47	7-20	2-22
(+)-PD Lactone	3	62	8-27	1-17

JOC 2015

OL 2012

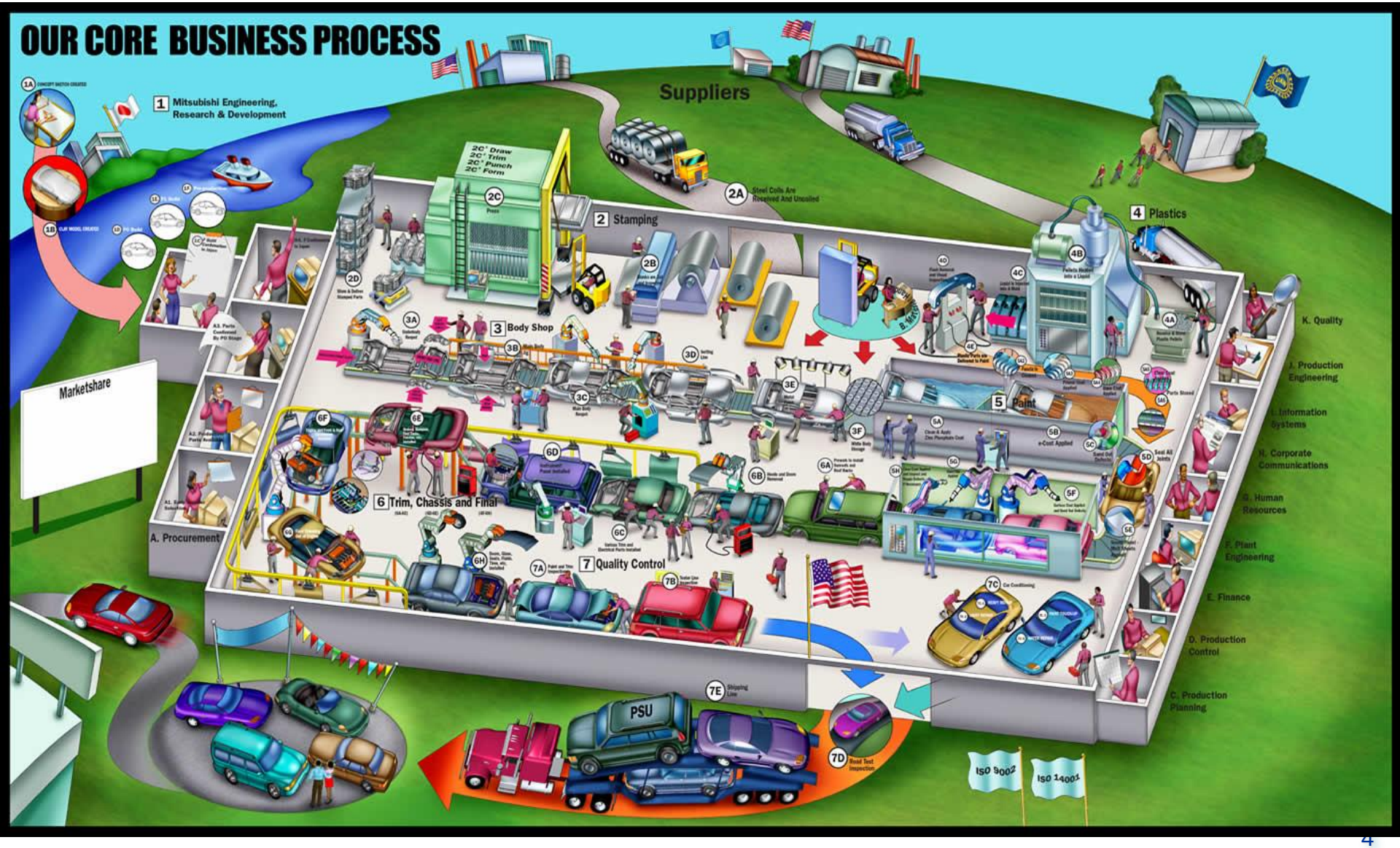
What controls selectivity?

Generalized mechanism proposed by Heck and Breslow in *1961* (for $HCo(CO)_4$):

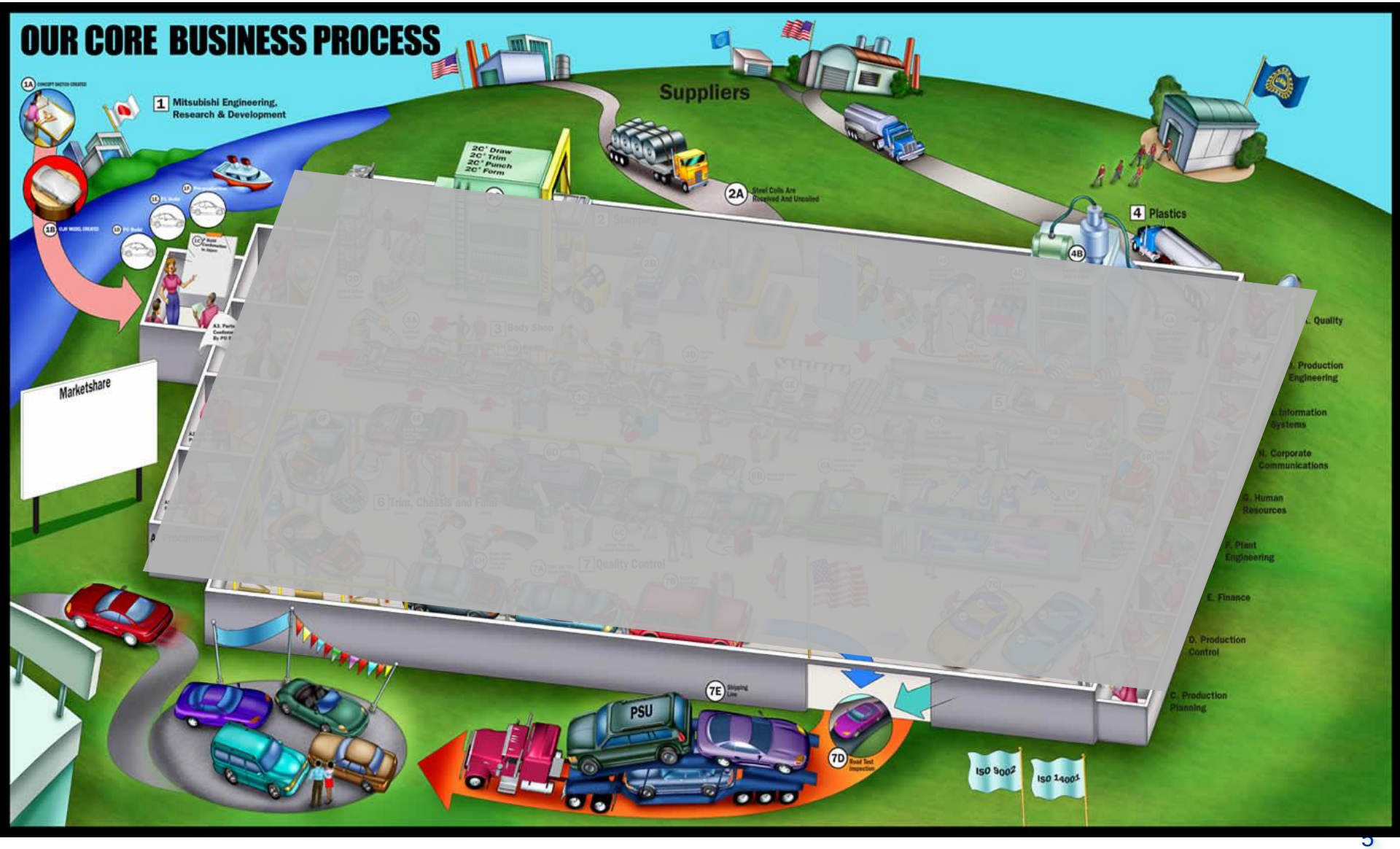


Outside-In vs. Inside-Out Approaches

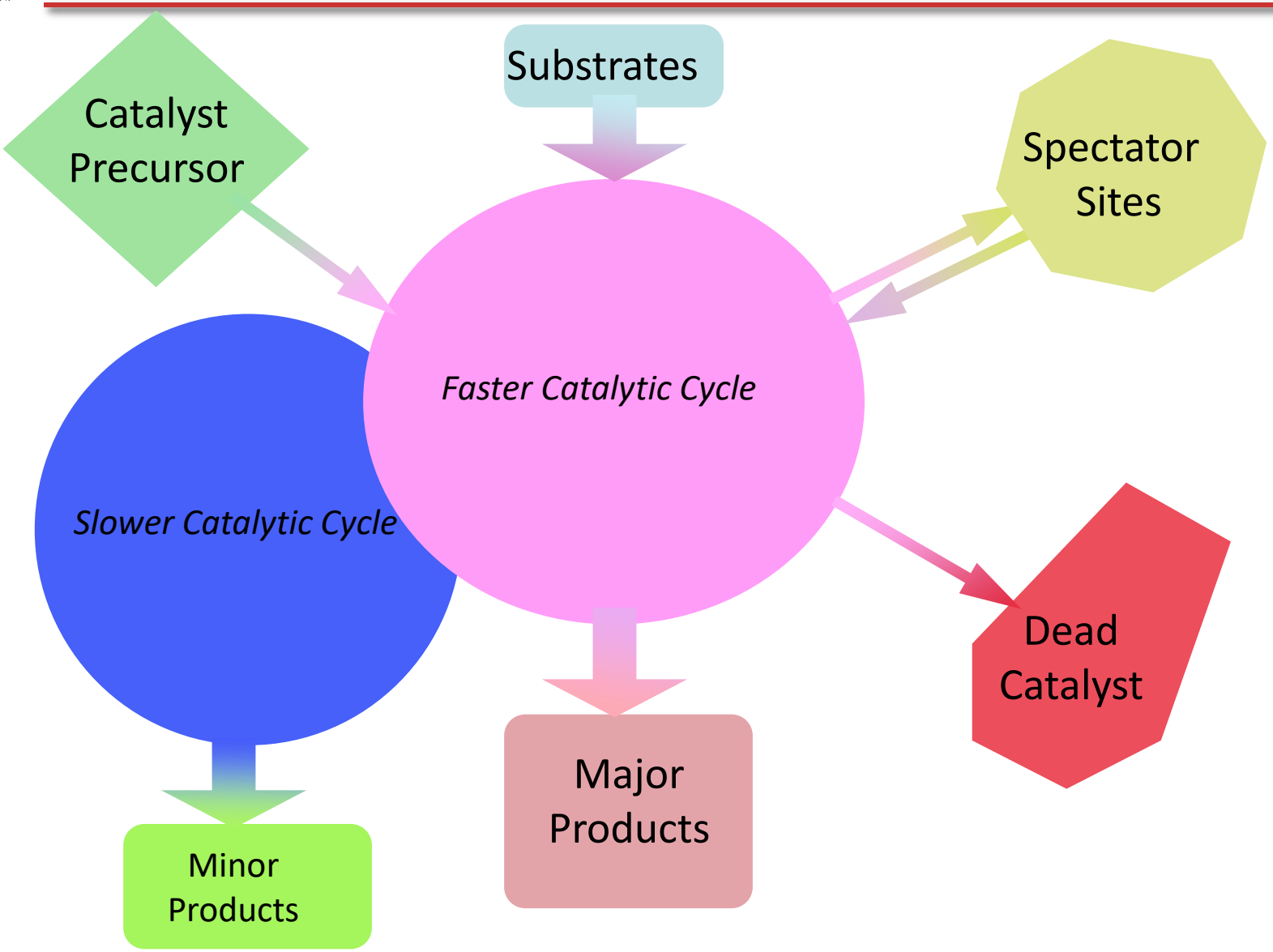
Industrial Spy Analogy to Mechanistic Study



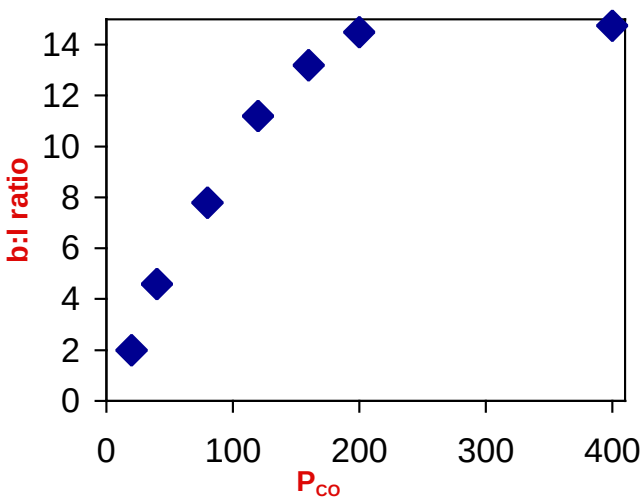
Industrial Espionage Analogy to Mechanism

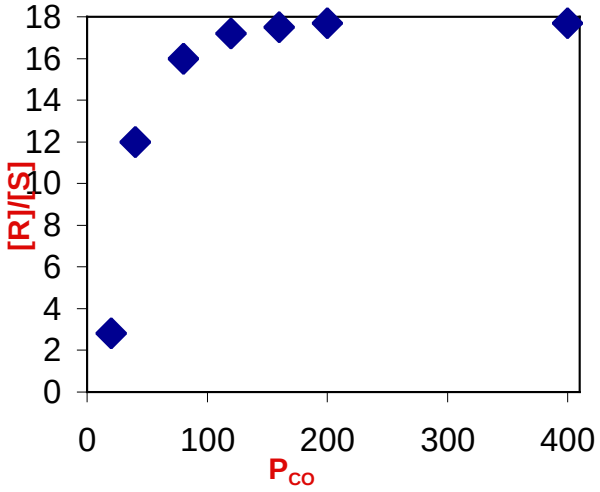


Mechanistic Studies – Outside-In

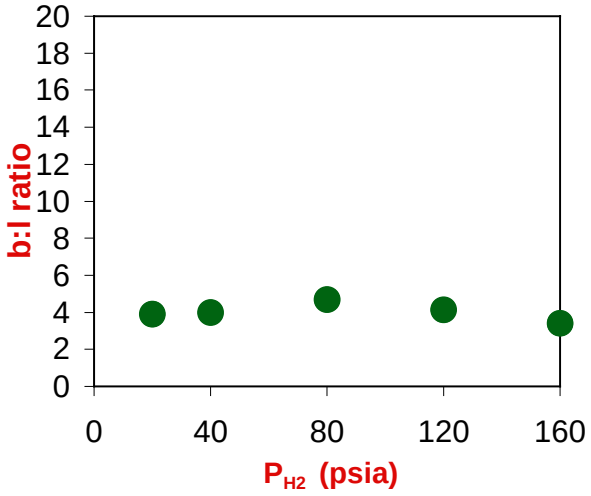


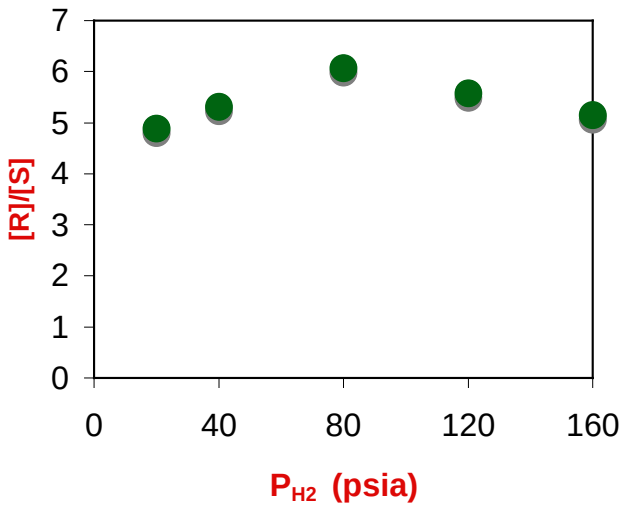
AHF of Styrene: Pressure Effects





- H_2 pressure 80 psia





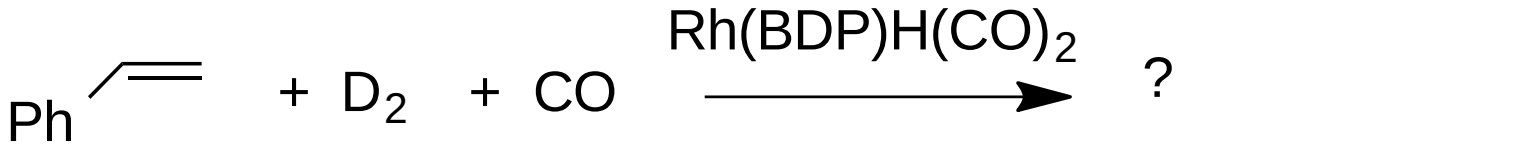
- CO pressure 40 psia

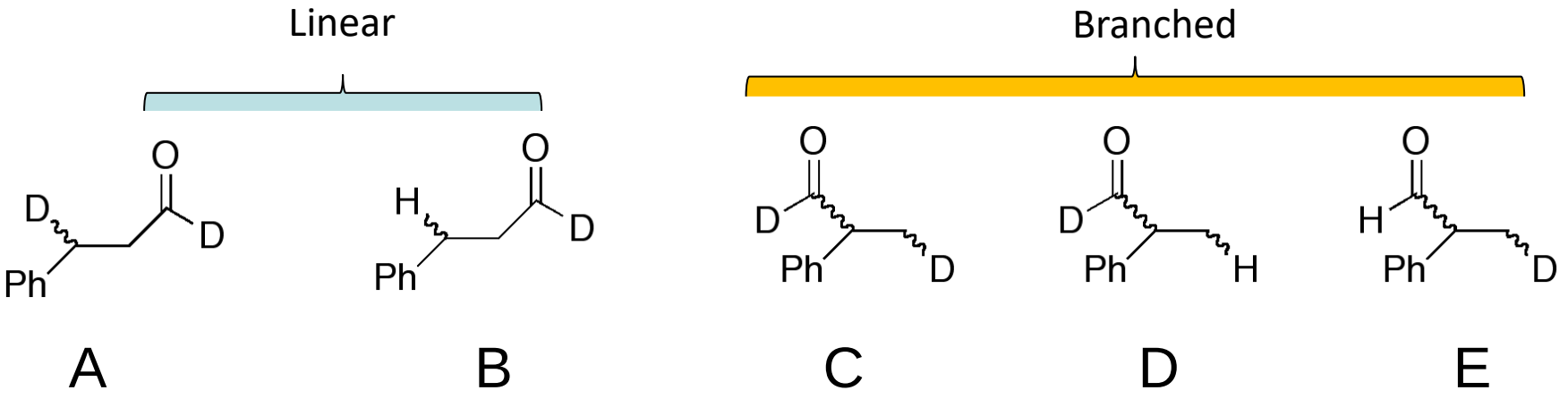
CO influence: Strong

H_2 influence: Weak

Predict the primary product with D_2/CO

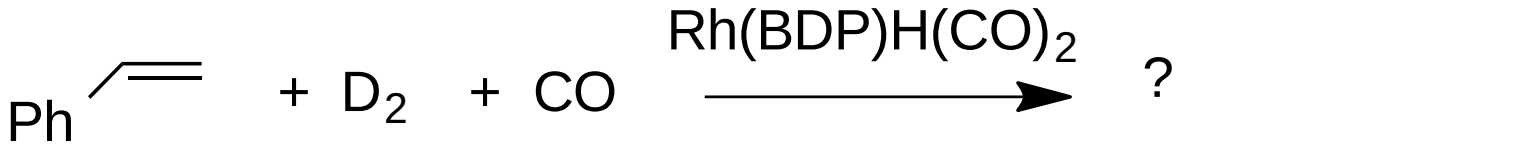
In the deuterioformylation (D_2/CO) of styrene performed to 10% conversion, which product will be most abundant?

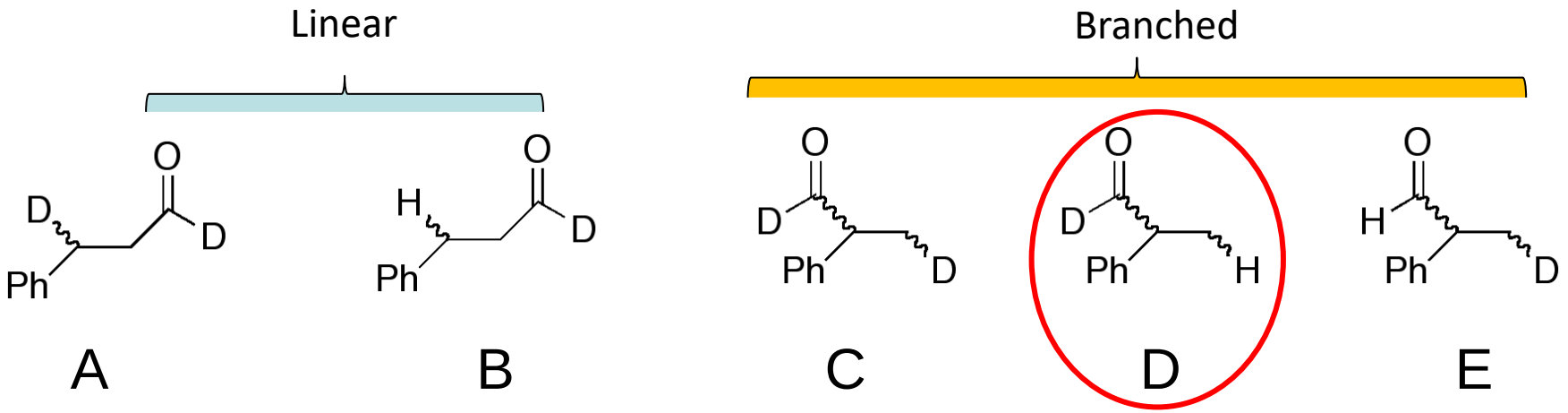




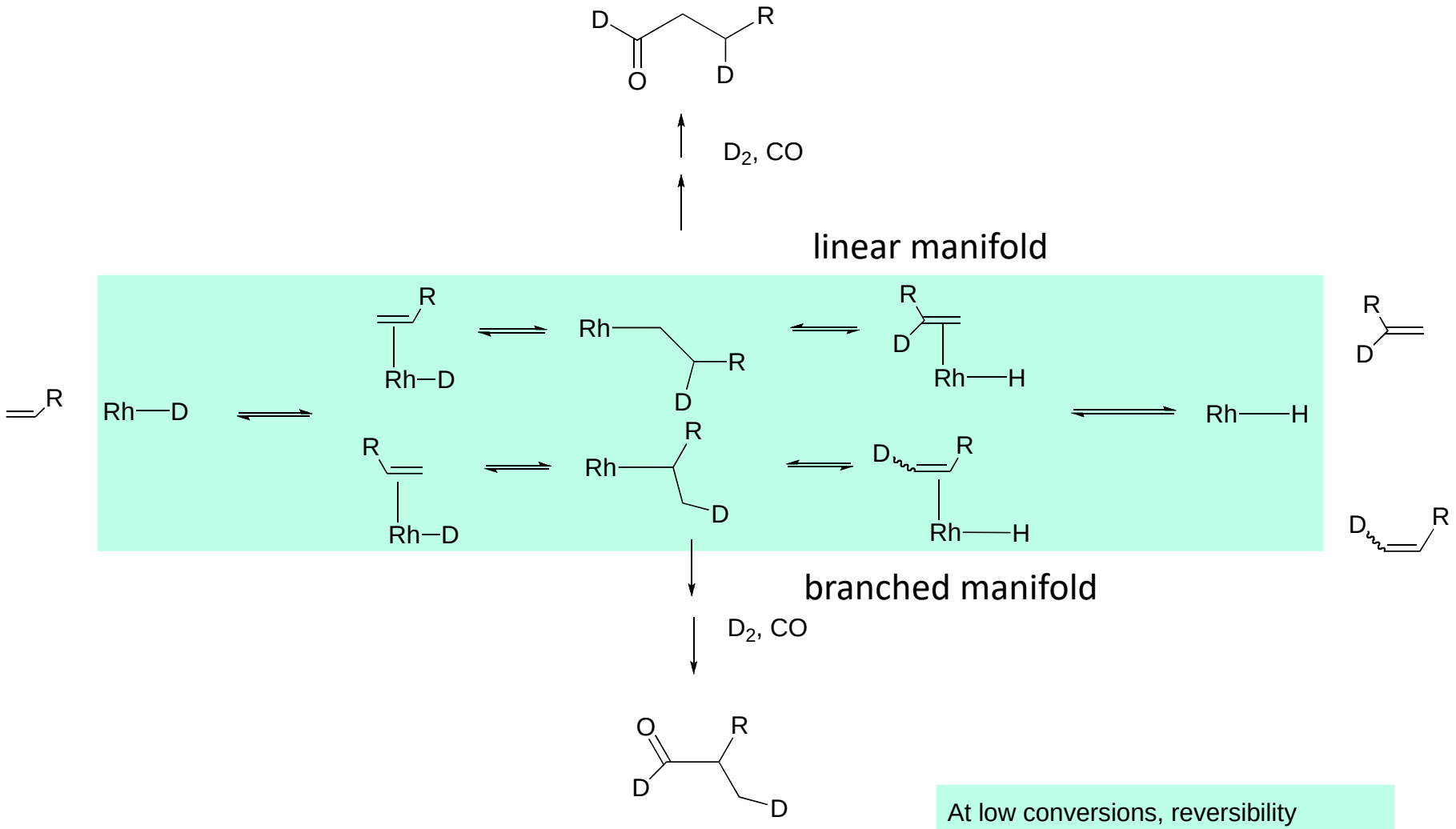
Predict the primary product with D_2/CO

In the deuterioformylation (D_2/CO) of styrene performed to 10% conversion, which product will be most abundant?





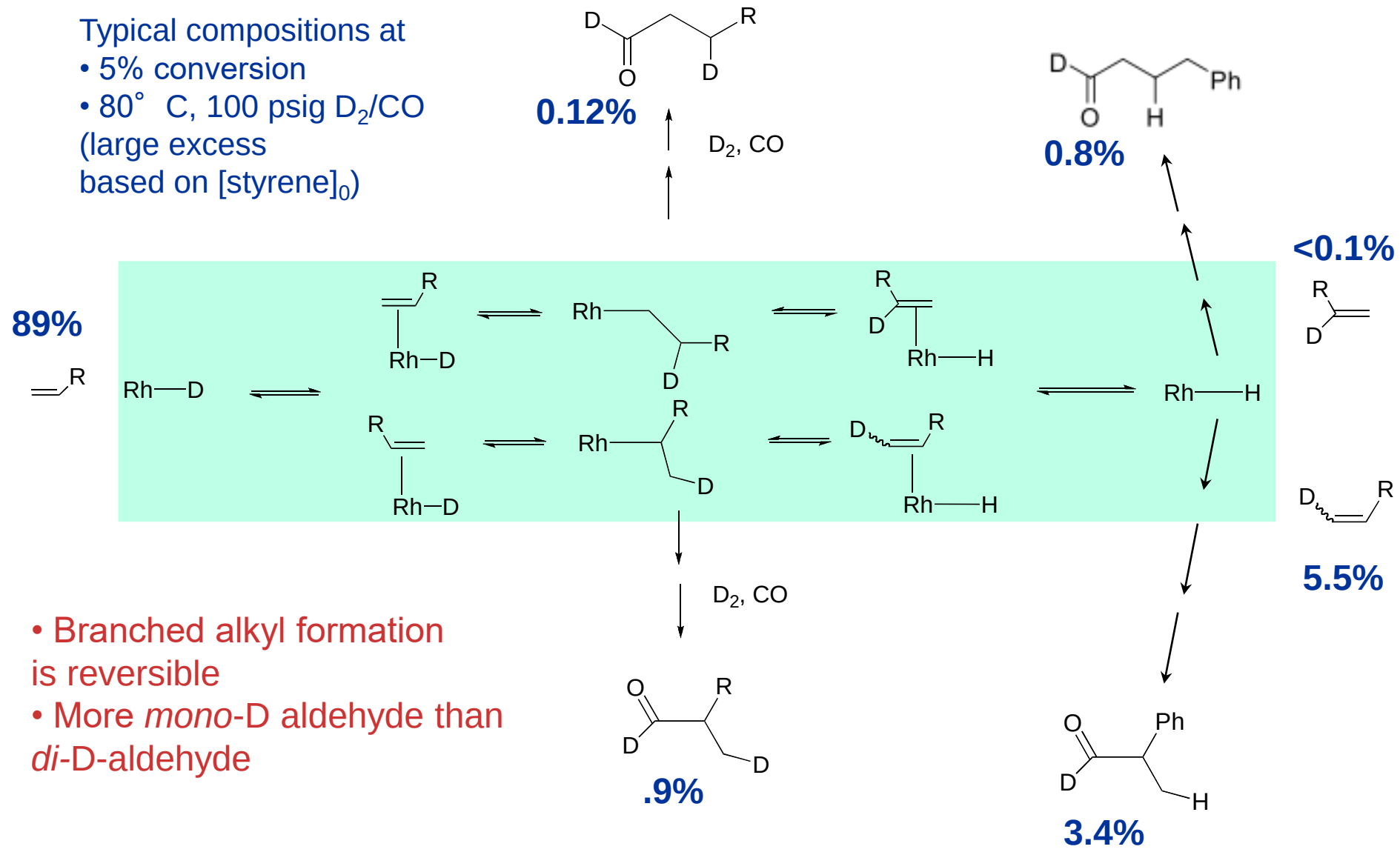
Hydroformylation with D_2



At low conversions, reversibility effects exchange of D into unreacted alkene

Styrene Deuterioformylation

Typical compositions at
- 5% conversion
- 80° C, 100 psig D_2/CO (large excess based on $[styrene]_0$)



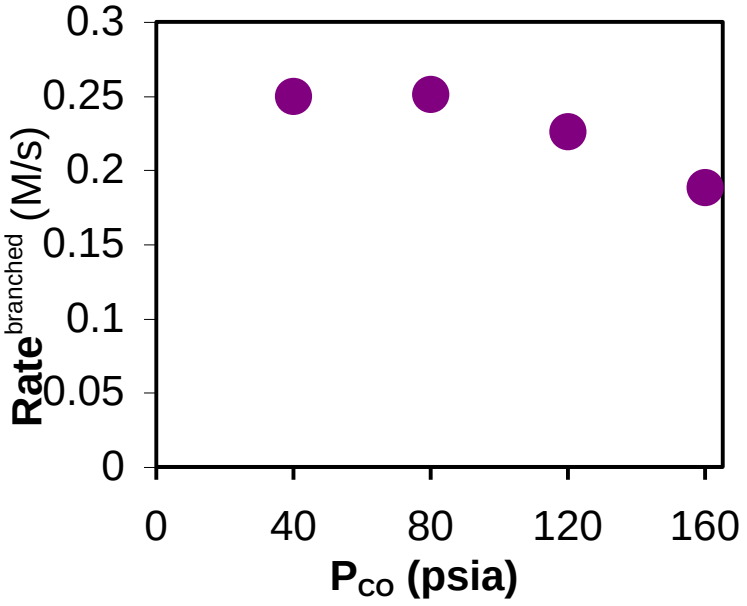
- Branched alkyl formation is reversible
- More *mono*-D aldehyde than *di*-D-aldehyde

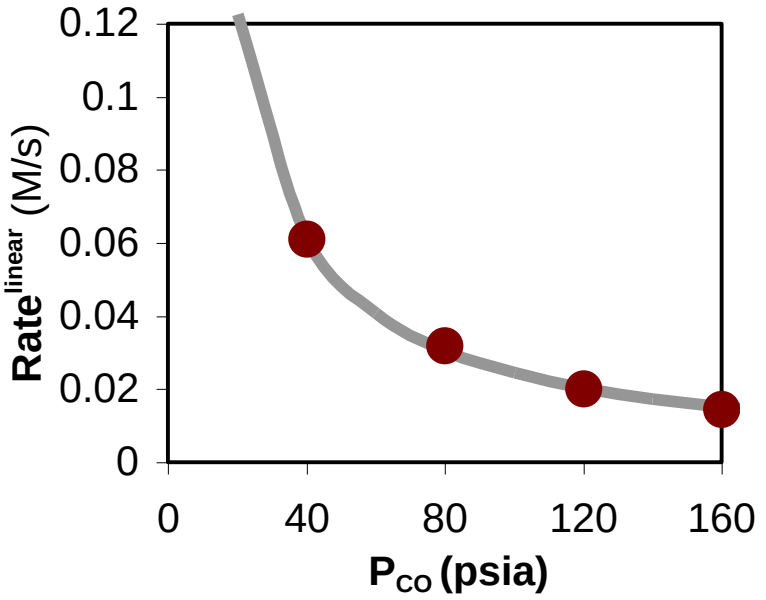
Linear & Branched Product Rate Laws

80° C
$[styrene]_0$=1.0 M
80psia H_2

$Rate_{linear} = k_{linear}[styrene][Rh]$
$Rate_{branched} = k_{branched}[styrene][Rh]$

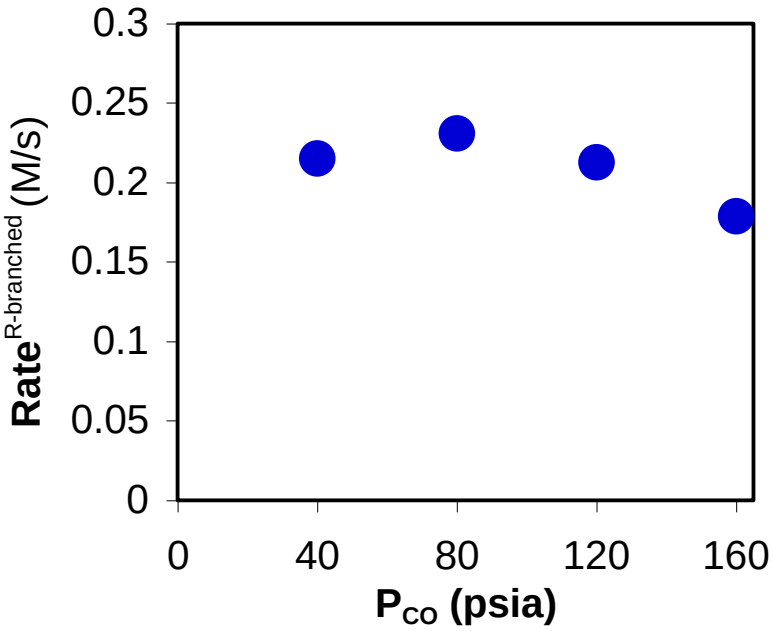
- Linear – Strong CO inhibition
- Branched – transforms from independent to inhibited by CO
- Branched:Linear Ratio 〈 P_{CO}

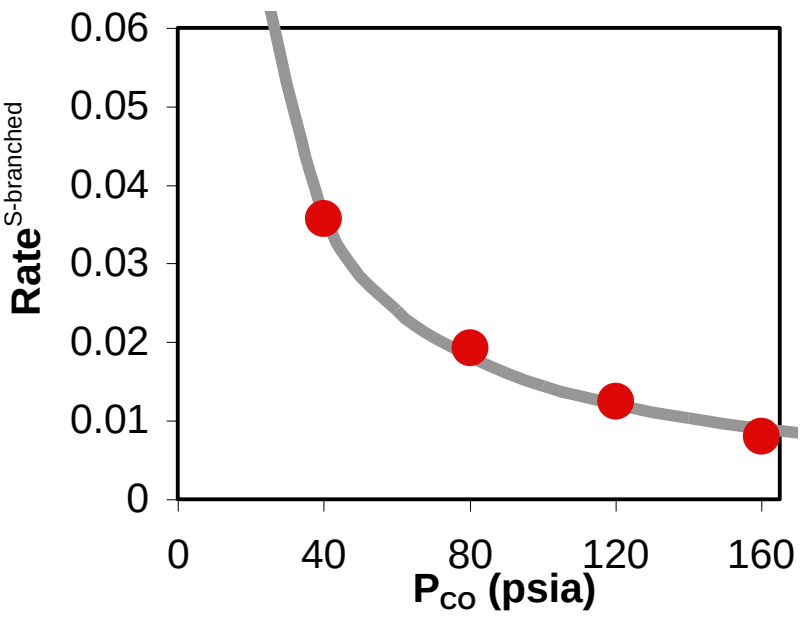




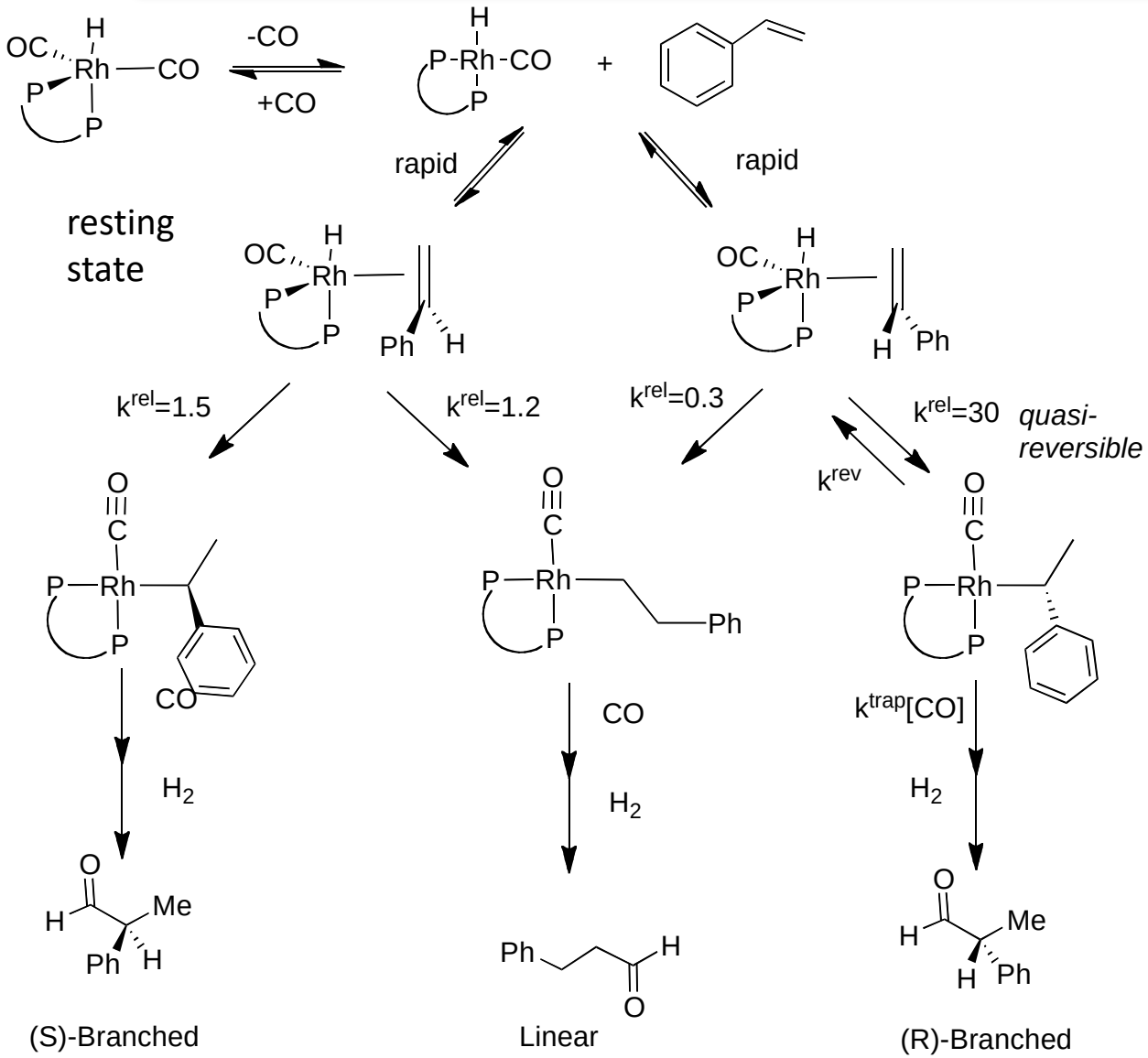
Rates for *R*- & *S*- Branched Products

80° C
$[styrene]_0$=1.0 M
80psig H_2





Origins of Selectivity



- CO inhibits reaction

$$\text{Rate} \propto \frac{1}{[CO]}$$

- From Pro-R enantioface, insertion is highly regioselective but partially reversible from R-Branched alkyl

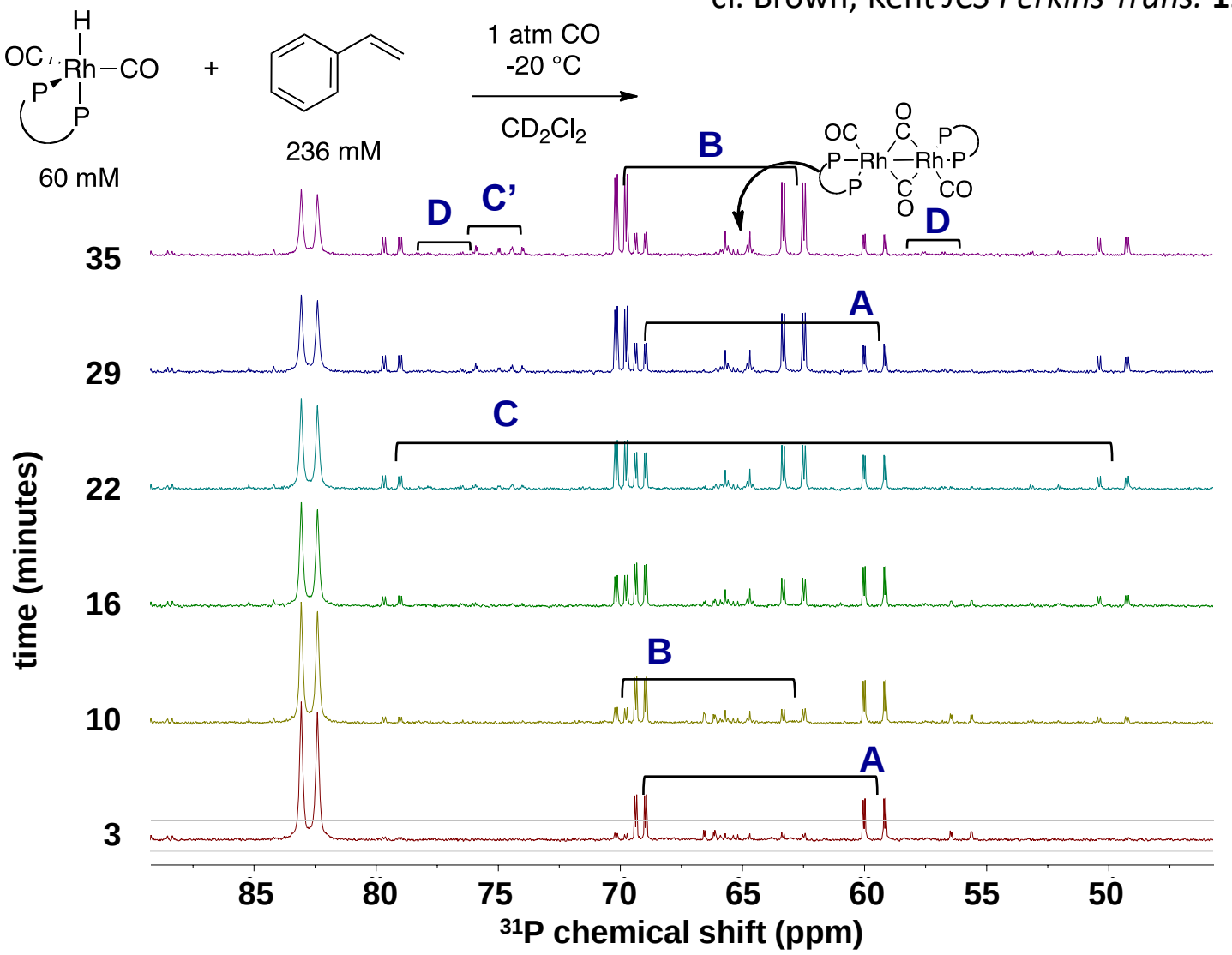
- From Pro-S enantioface, insertion is not regioselective

- CO promotes trapping of R-Branched alkyl

$k^{trap}/k^{rev} \approx 0.01\ psi^{-1}s^{-1}$

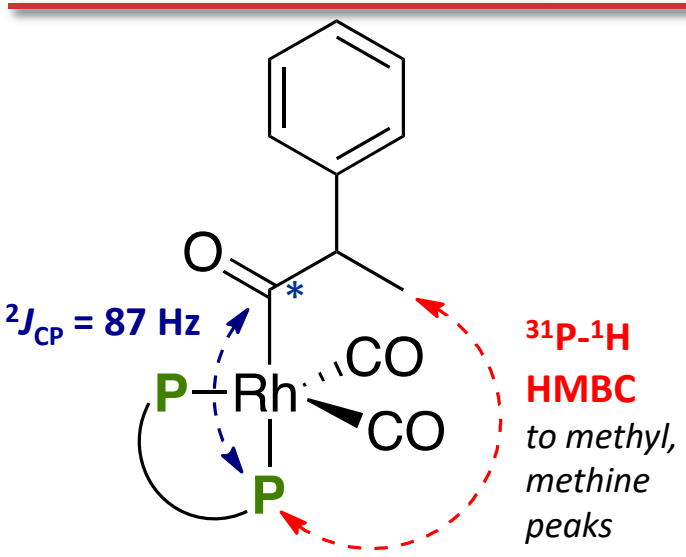
Direct Observation: Low T, Low P

cf. Brown, Kent *JCS Perkins Trans.* **1987**, 1597-1607.

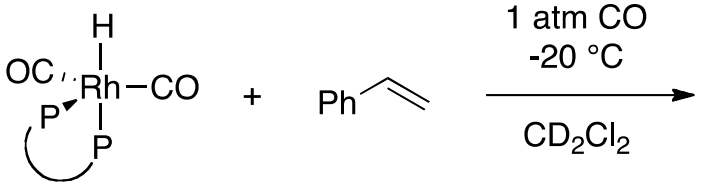


Eleanor Nelsen

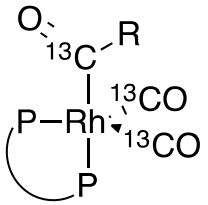
Branched Acyl Complex - A



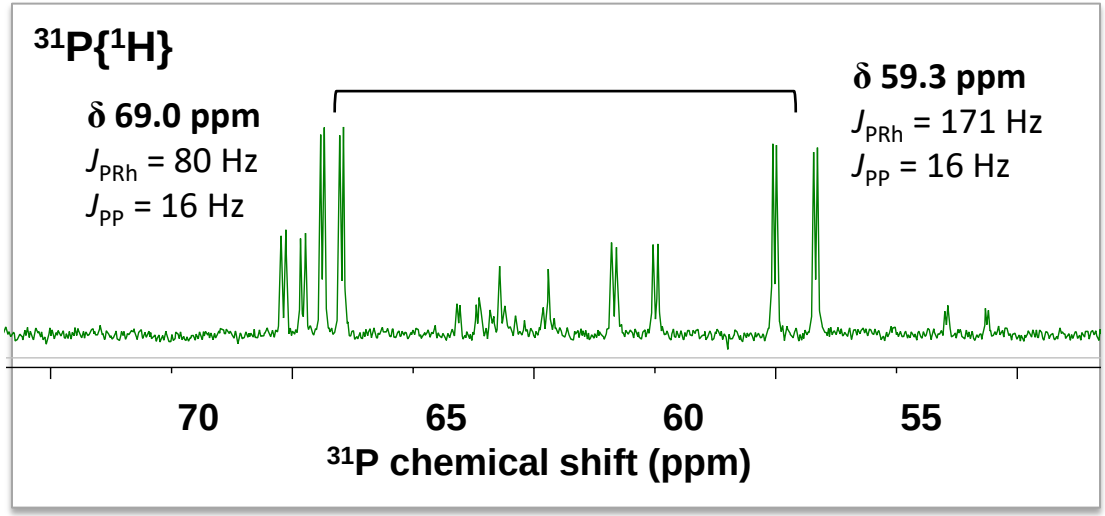
- **Kinetic product** of

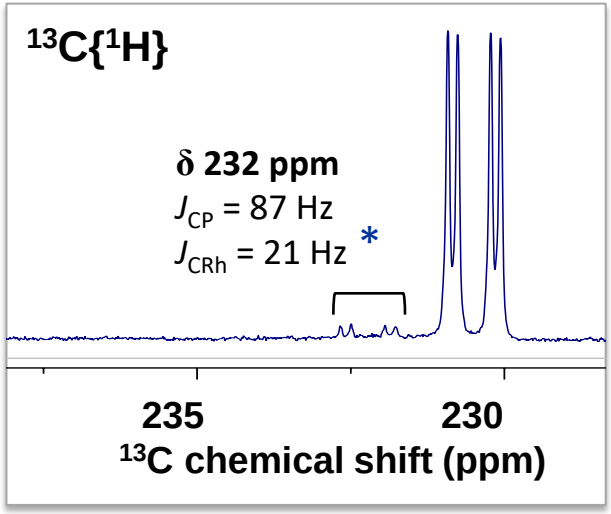


- Exchange of axial, equatorial phosphorus atoms slow.
- Coordination number, geometry determined measuring $^2J_{PC}$ of



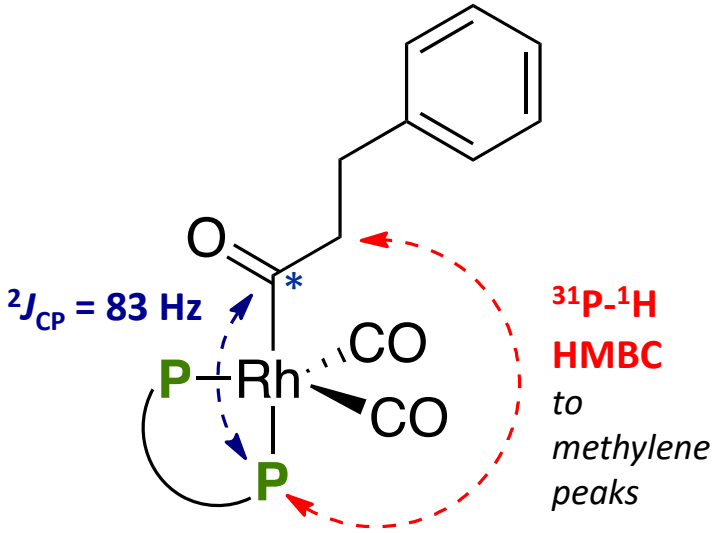
by



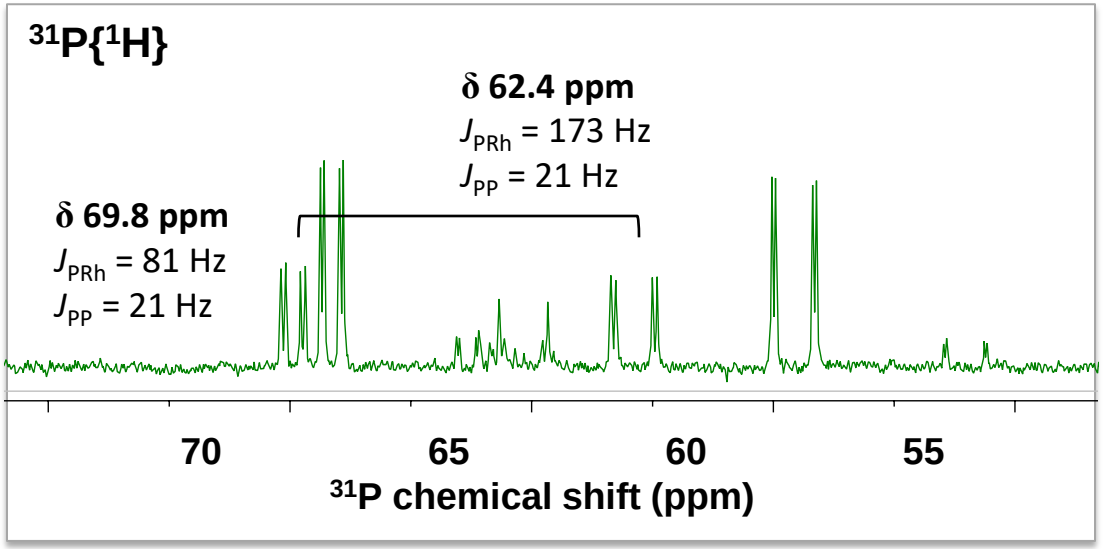


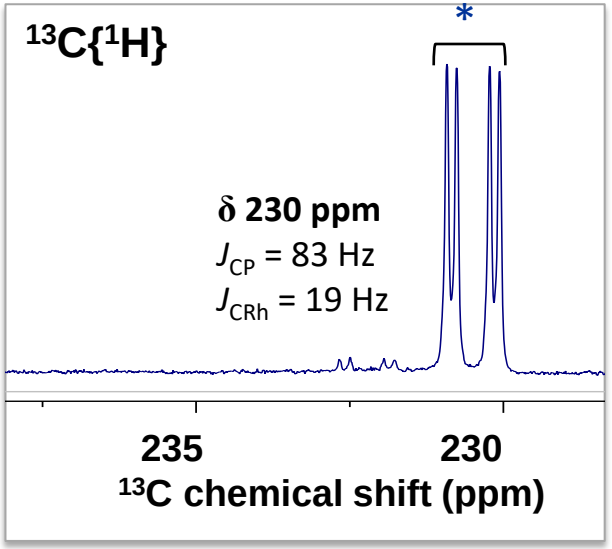
Eleanor Nelsen

Linear Acyl Complex - B



- **Slower rate of formation** than branched acyl (1:10)
- **Thermodynamically preferred** regioisomer (30:1) at -20 ° C
- Exchange of axial, equatorial phosphorus atoms slow
- Coordination number, geometry determined using ^{13}CO





Eleanor Nelson

In-Situ High Pressure NMR

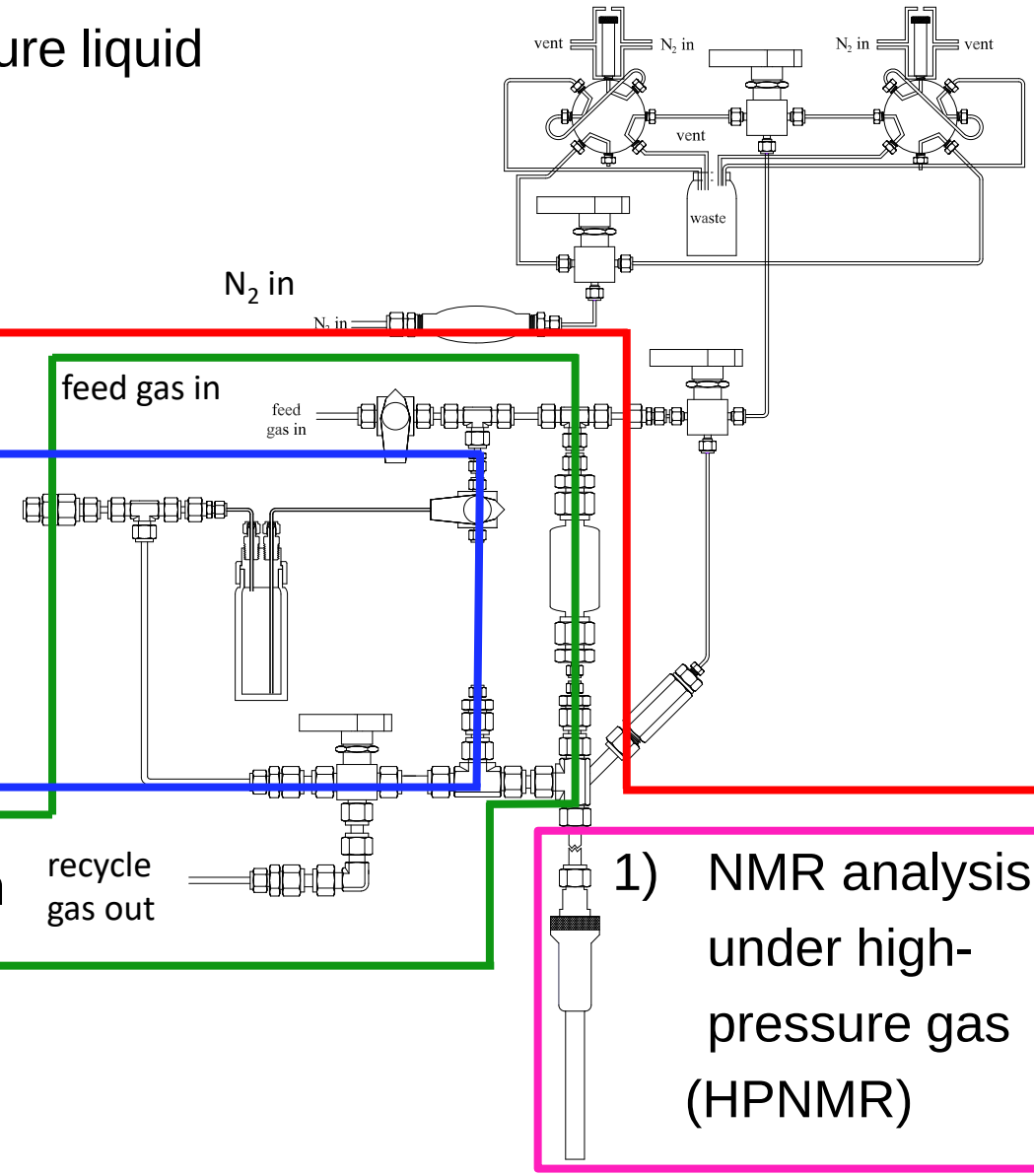
- NMR is the most information-rich technique for catalysis by diamagnetic organometallics
- High Pressure NMR suffers from slow gas-liquid mass transport

Ideally we would use NMR

- As a high throughput device
- Under common reaction pressures and temperatures
- With excellent gas-liquid mixing
- To simultaneously monitor product formation and catalyst speciation as a function of time

WiHP-NMRR (Wisconsin High Pressure NMR Reactor)

3) High-pressure liquid injection

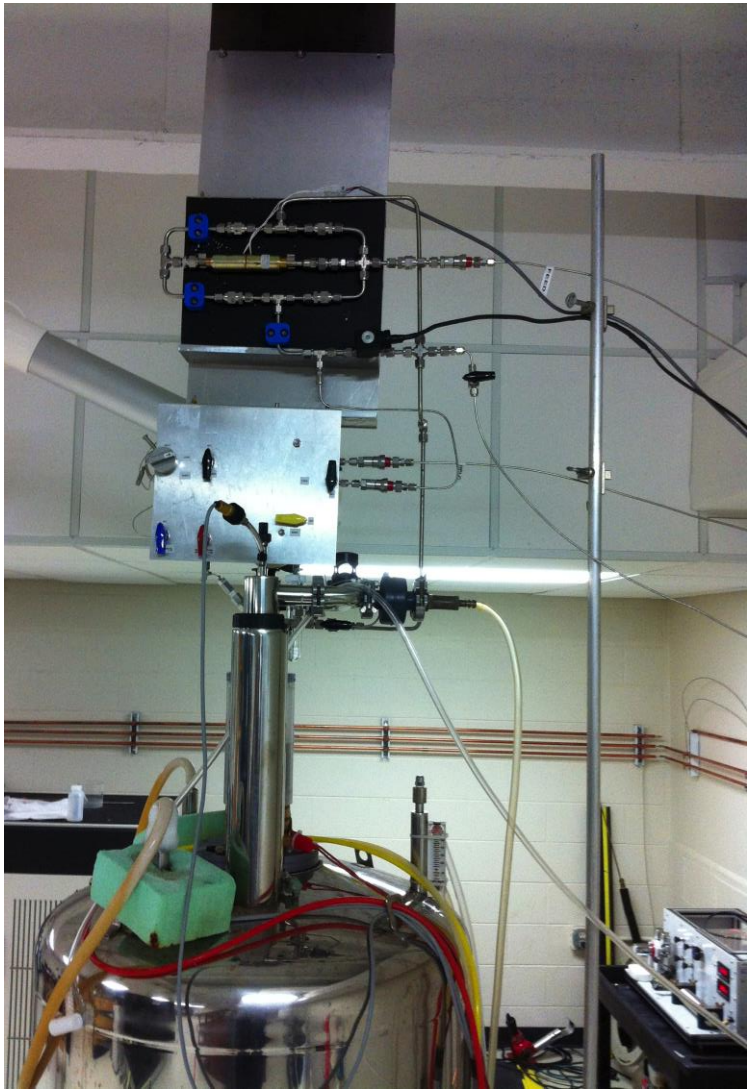


4) Wash system

2) Gas circulation

1) NMR analysis under high-pressure gas (HPNMR)

WiHP-NMRR (Wisconsin High Pressure NMR Reactor)

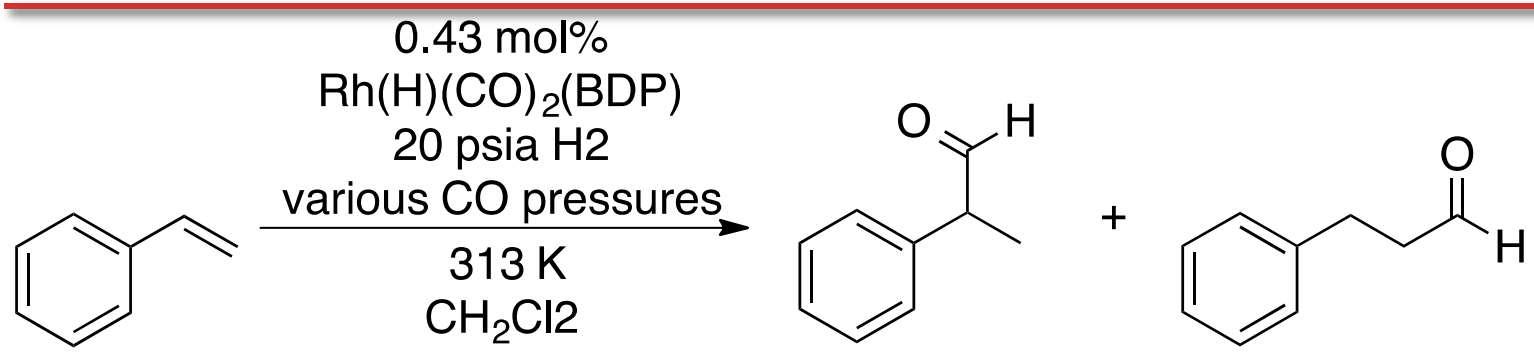


Nick Beach
Spring Knapp

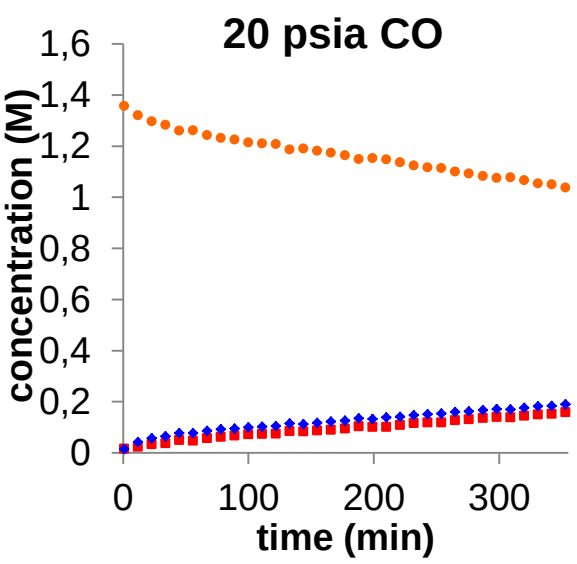
Rapid Injection in WiHP-NMRR

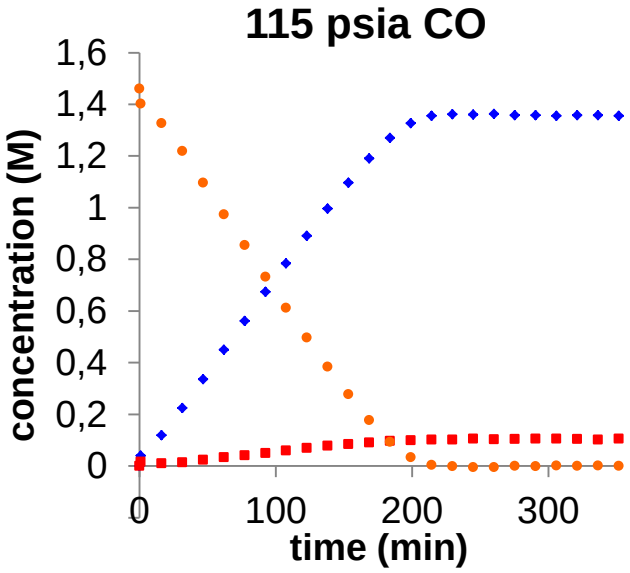
Spring Knapp

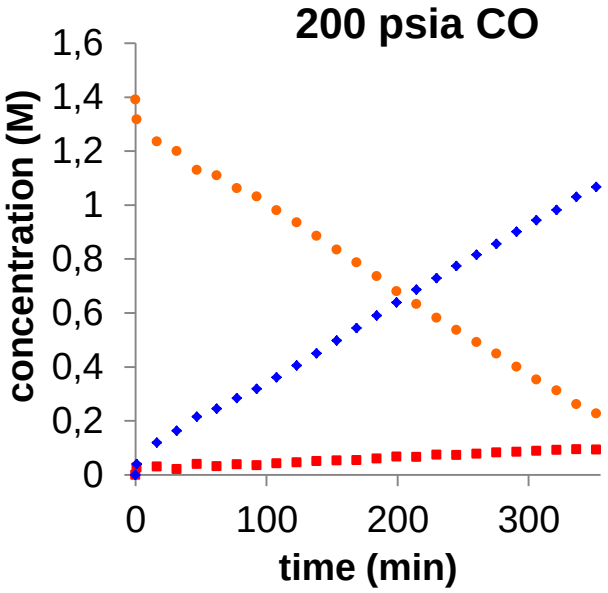
In Situ NMR: Styrene Hydroformylation



styrene branched linear

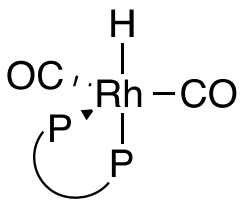




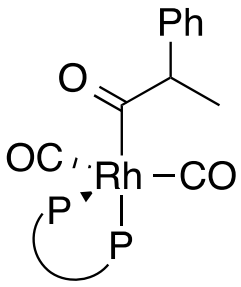


Anna Brezny

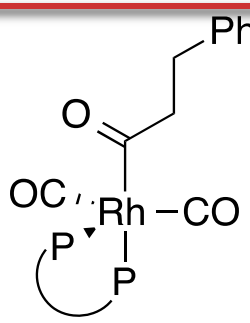
Catalyst Speciation (20psia H_2, 313K)



1 ▲

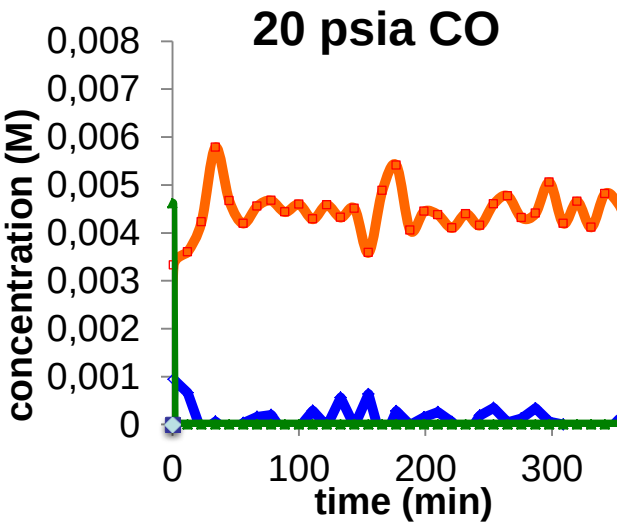


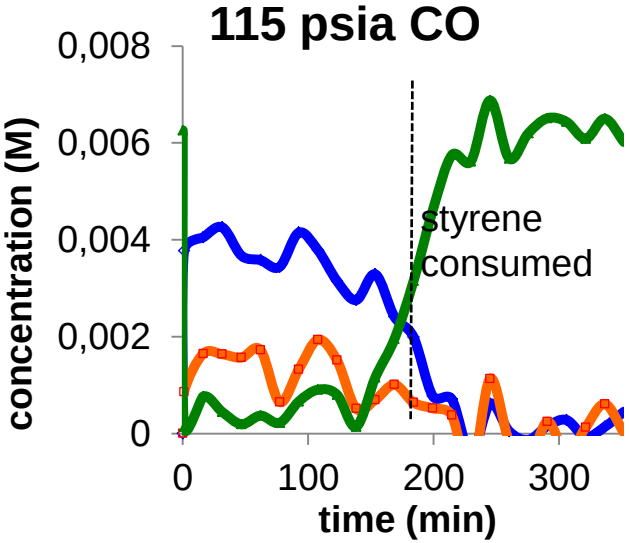
7b ◇

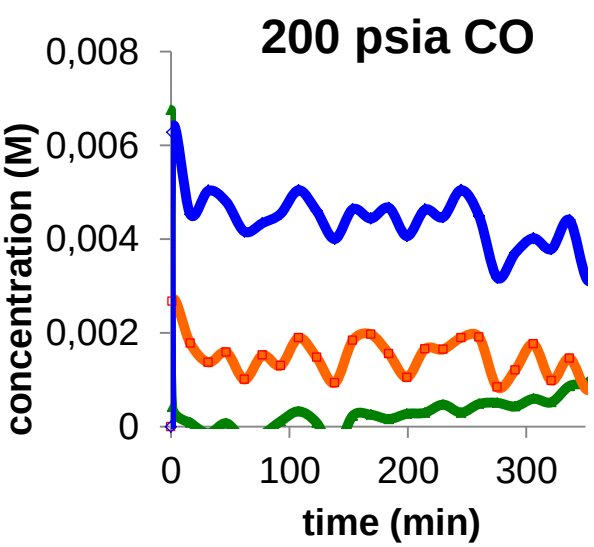


7l □

Linear acyl resting state gives
1:1 branched:linear product







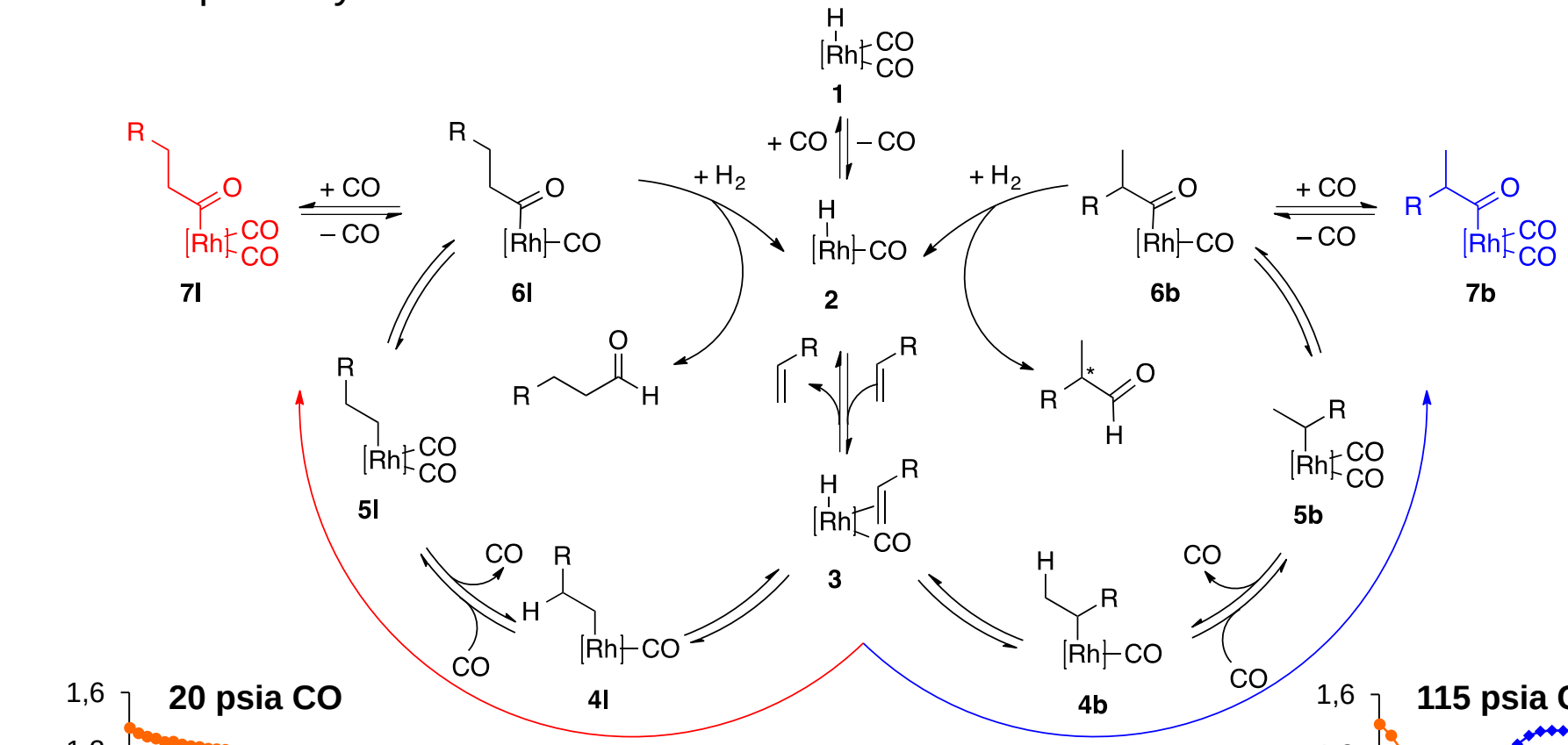
Resting state = linear acyl | branched acyl | branched acyl

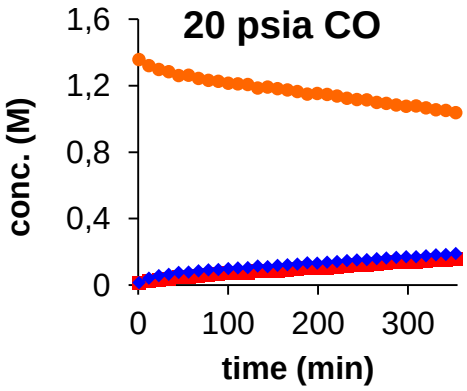
Aldehyde product: b:l = 1:1 | b:l = 20:1 | b:l = 20:1

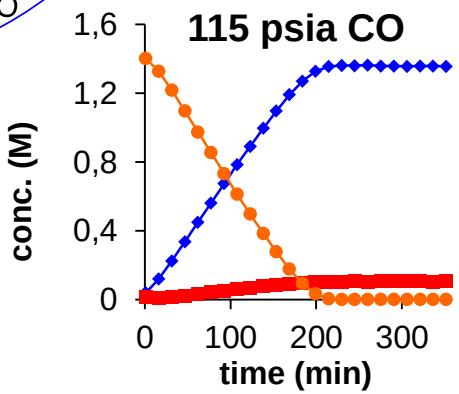
Rate = slow | fast | medium

More than one step is important...

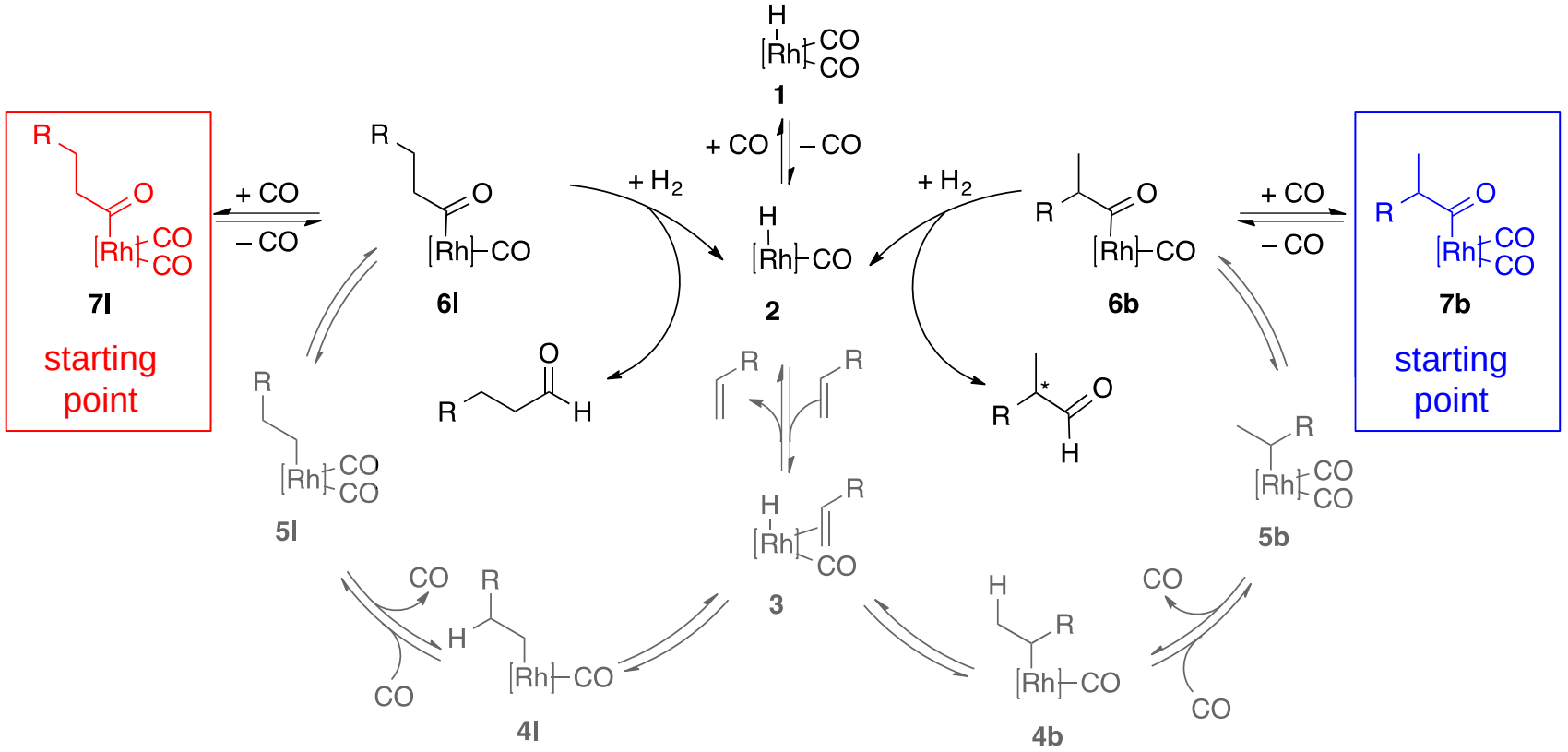
- At low CO pressure, more catalyst enters the slower, but thermodynamically favored, linear pathway



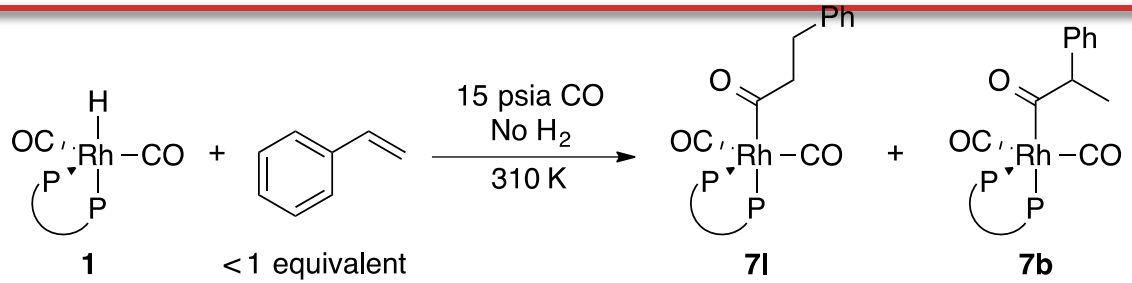


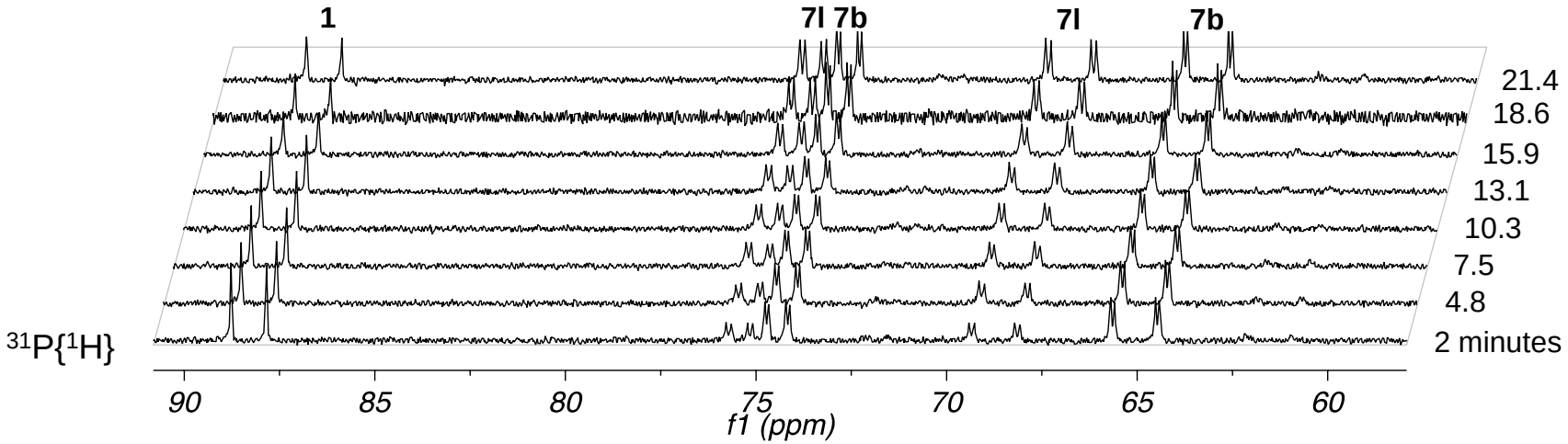


Catalytic versus Non-Catalytic Reactions

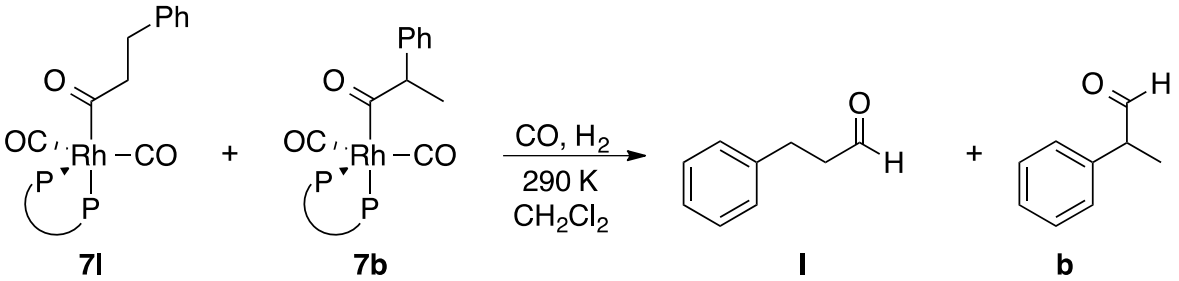


Hydrogenolysis Experimental Setup

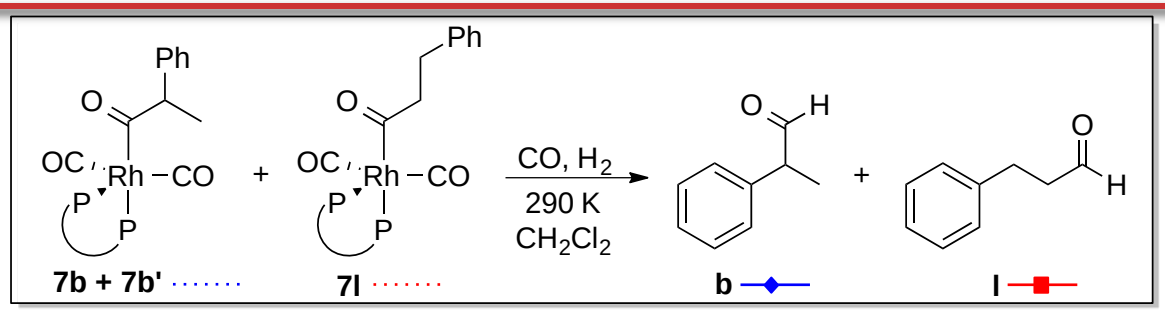


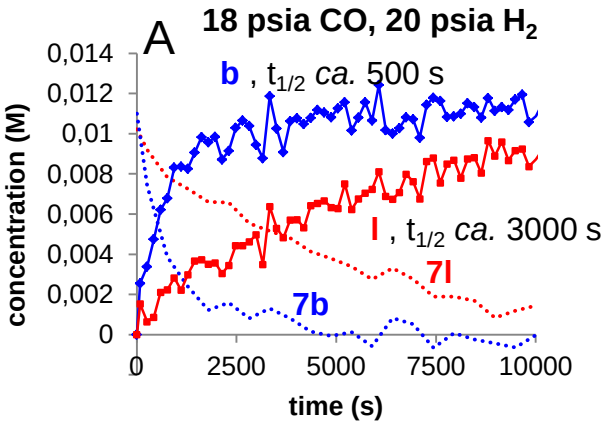


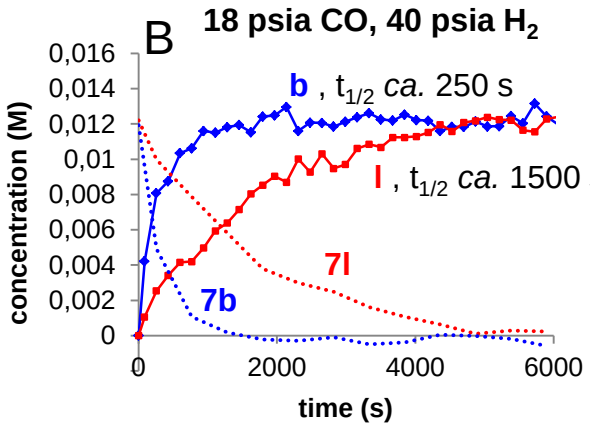
After **7b**:**7l** = 1:1, cool reaction spectrometer to 290 K.
Add CO to desired pressure. Add H_2; start collecting $^{31}P\{^1H\}$ and ^1H spectra

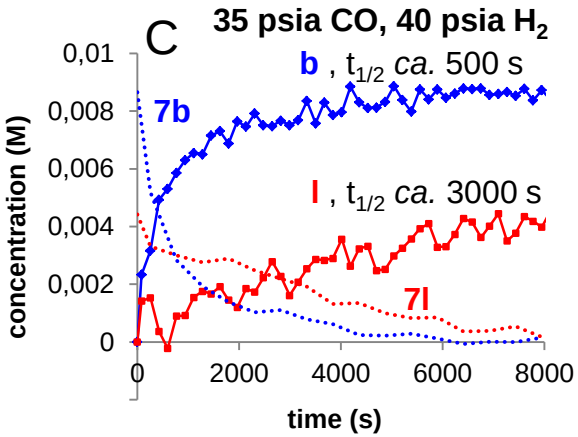


Exploring Non-Catalytic Hydrogenolysis Rates



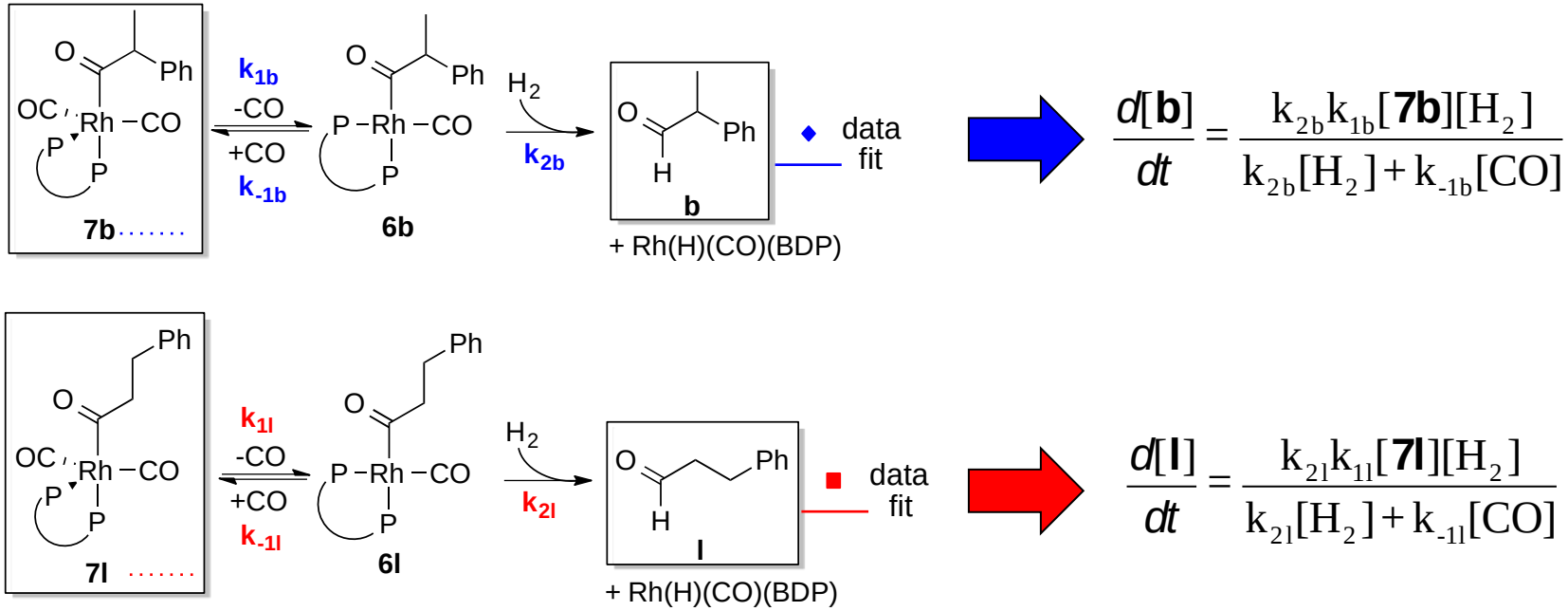






- Data collected at 3 CO pressures (18, 35, 70 psia) and a wide range of H_2 pressures (20-720 psia)
- No isomerization between **7b** and **7l** observed
- Saturation behavior in [H_2]
- First order inhibition on [CO]

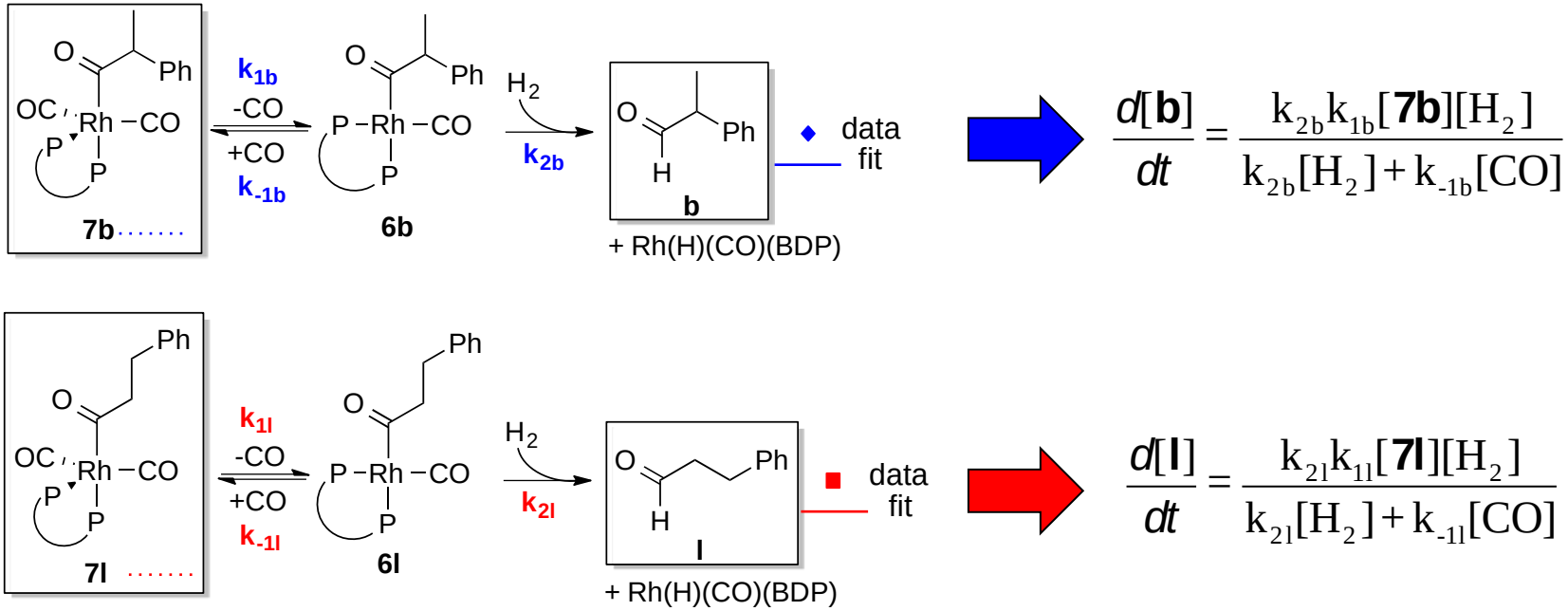
Global Fitting in COPASI

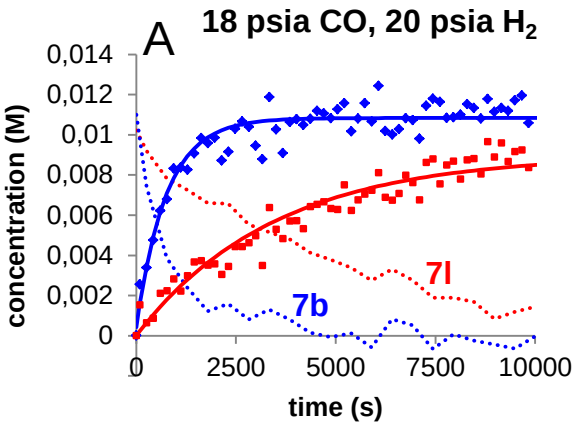


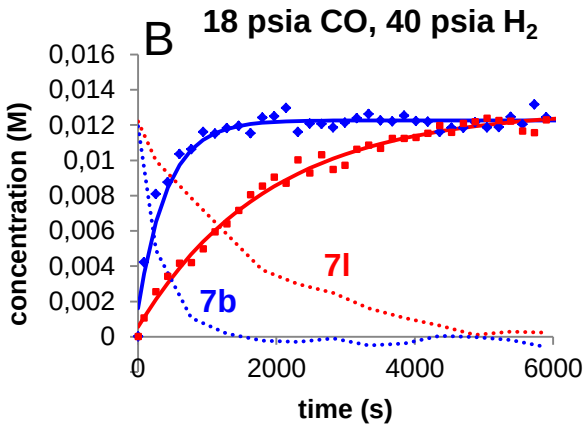
- 4 adjustable parameters to fit 40 experiments
  - k_{1b}
  - k_{1l}
  - k_{-1b}/k_{2b}
  - k_{-1l}/k_{2l}
- Give the model [CO], $[H_2]$, $[b]_t$, $[l]_t$ for each reaction
- Computes one set of parameters to best fit all experimental data

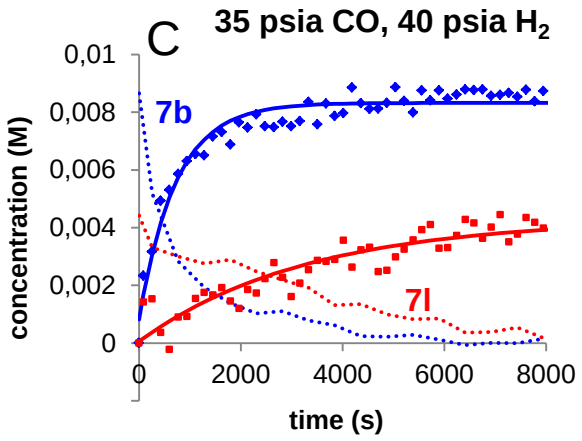
COPASI: Hoops, S.; Sahle, S.; Gauges, R.; Lee, C.; Pahle, J.; Simus, N.; Singhal, M.; Xu, L.; Mendes, P.; Kummer, U. *Bioinformatics* **2006**, *22*, 3067.

Modeling Hydrogenolysis

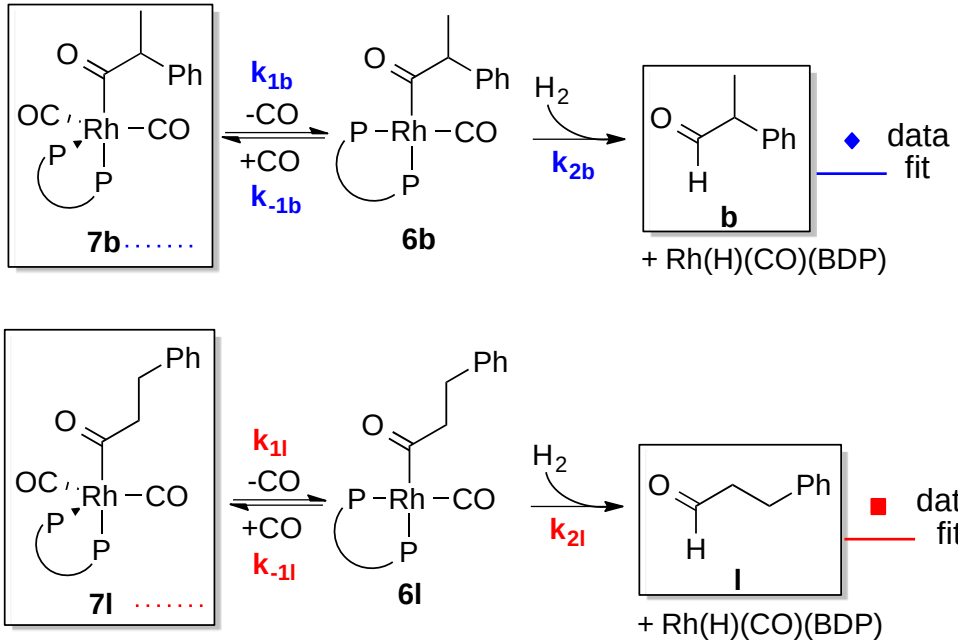








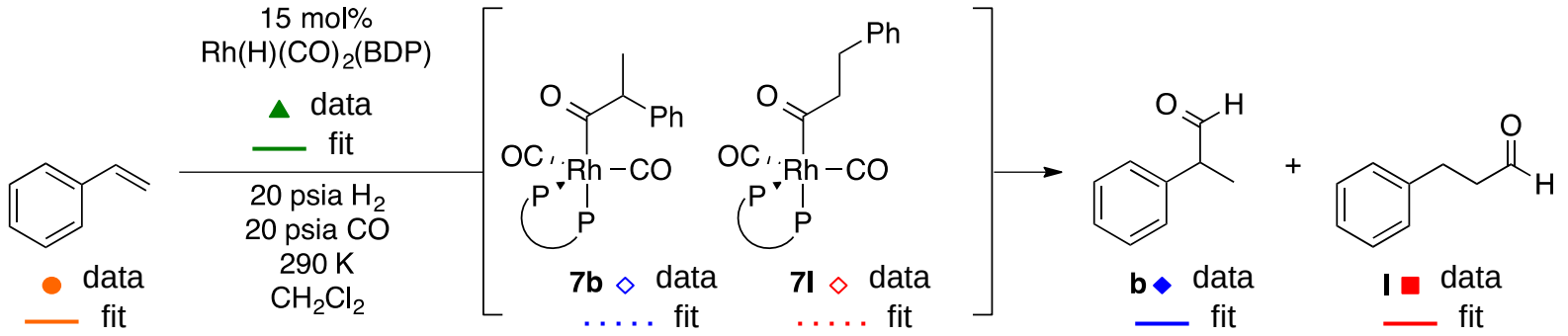
Kinetic Parameters for Hydrogenolysis

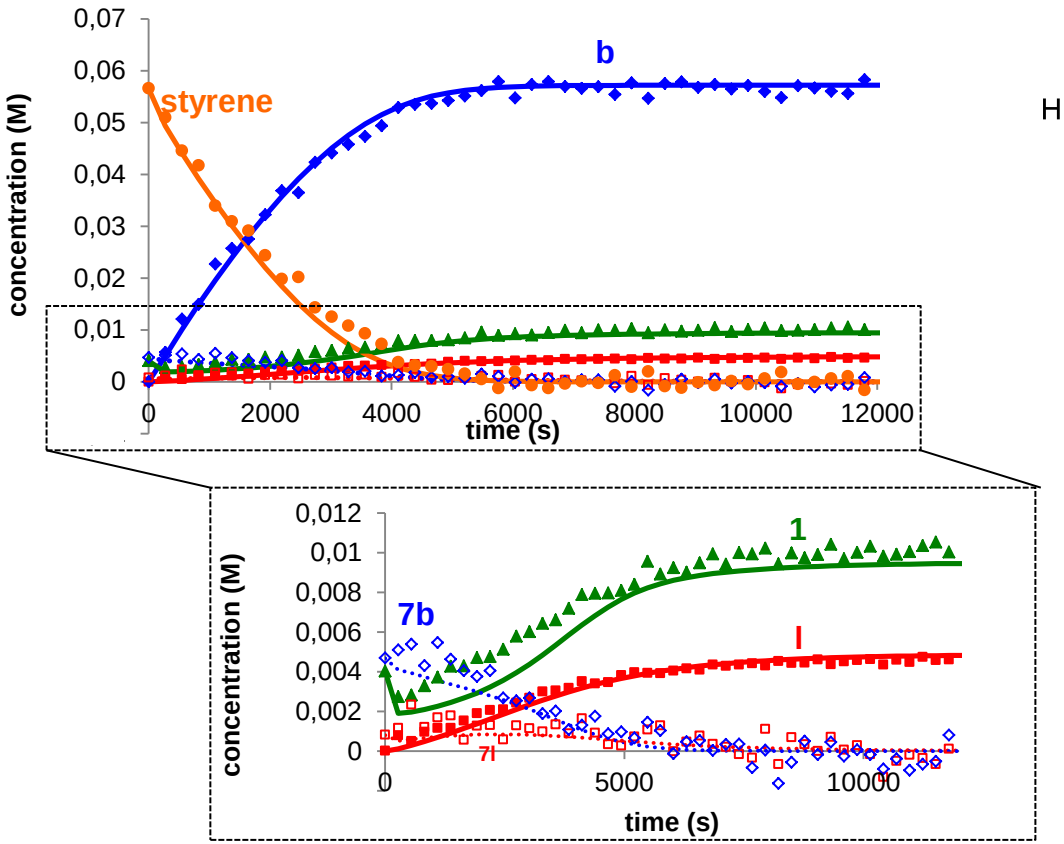


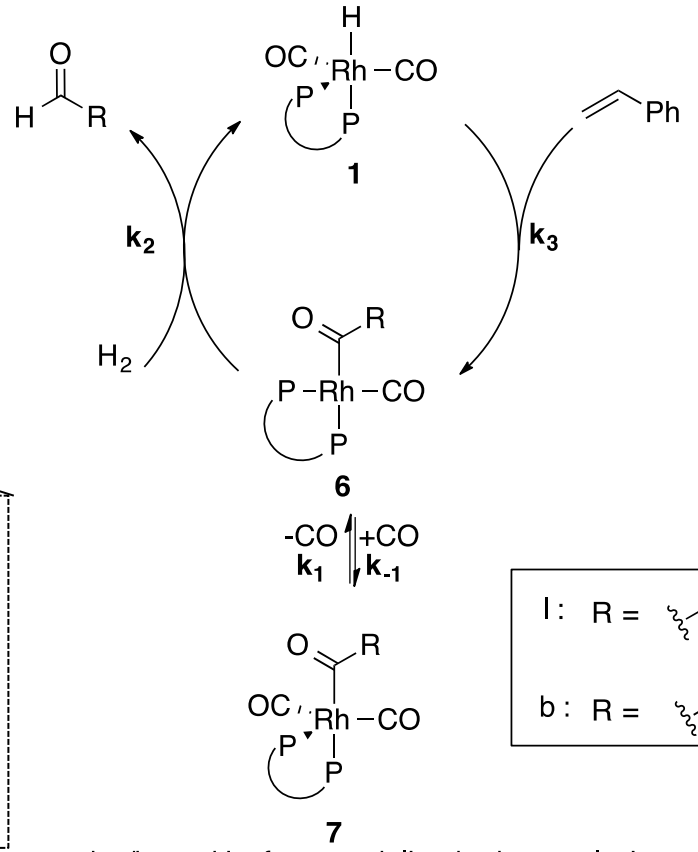
	Value	Standard Deviation
k_{1b}	2.3 x10^{-2} (s^{-1})	1 x10^{-3}
k_{1l}	6.4 x10^{-3} (s^{-1})	5 x10^{-4}
k_{-1b}/k_{2b}	8.2	0.2
k_{-1l}/k_{2l}	10.5	0.3

- **7b** dissociates CO 3.5x faster than **7l**
- Competition for binding CO versus reaction with H_2 similar for both **6b** and **6l**
- These differences alone cannot explain the drastic mismatch between catalyst speciation and product ratios in catalytic hydroformylation
- Catalytic data are at a different temperature than the hydrogenolysis experiments

Modeling Catalytic Data







l : R =

b : R =

k_{-1}/k_2 and k_1 from modeling hydrogenolysis

Is the Catalytic Rate = Rate of Hydrogenolysis of **7**?

- For the catalytic hydroformylation at 40 psia syn gas and 17 ° C:
  - $[\mathbf{7b}]_{SS}$ = 4.9 mM
  - $[\mathbf{7l}]_{SS}$ = 1.9 mM

- **Predicted rate of product formation:**

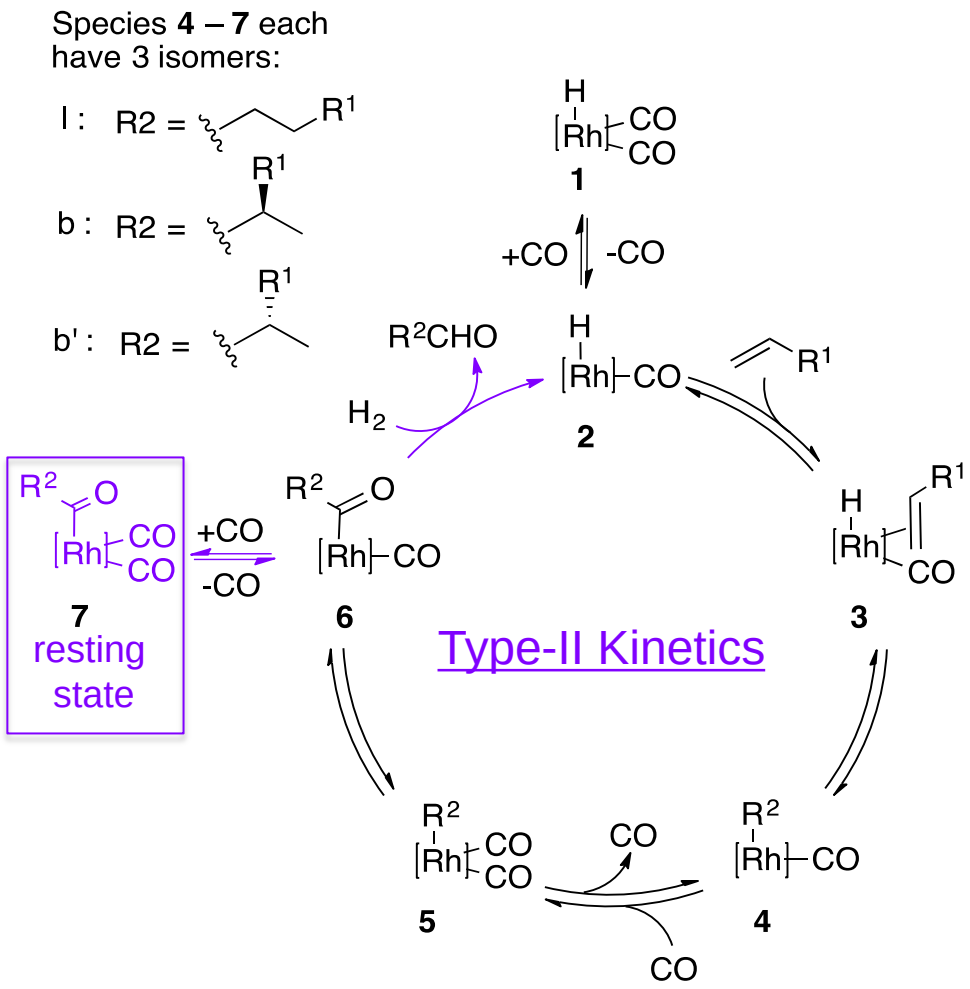
  $Rate_{br}$ = 5.2(2) x10^{-6} M/s

  $Rate_{lin}$ = 3.6(3) x10^{-7} M/s

- **Observed catalytic rates:**

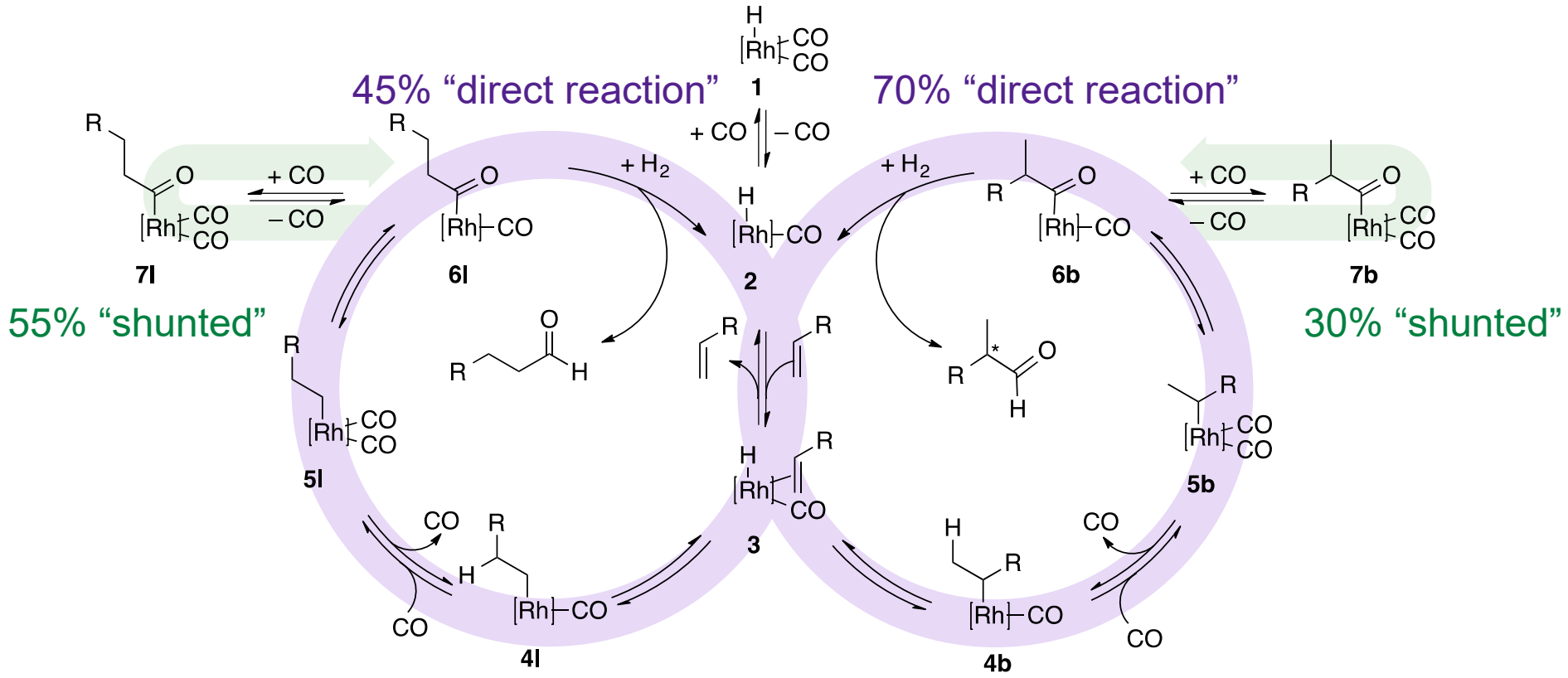
  $Rate_{br}$ = 1.8(1) x10^{-5} M/s **(3.5x)**

  $Rate_{lin}$ = 8.3(1) x10^{-7} M/s **(2.3x)**



$$Rate_{total} = Rate_{hydrogenolysis} + "excess"$$

Shunted versus Direct Pathways



- direct pathway contributes substantially to the overall rate even under conditions in which *all* of the *observable* catalyst is off-cycle

- inappropriate to identify the reaction as rate-limited by the hydrogenolysis of acyl dicarbonyls

Many thanks…

Students

Anna Brezny
Eleanor Nelson
Katie Ziebarth
Brad Jones
Floriana Foarta
Tom Clark

Postdocs

Nick Beach
Spring Knapp
Wiechang Jin

Collaborators

Jerzy Klosin (Dow)
Frank Neese
Rob Froese (Dow)
Eric Clot
Joe Martinelli (Eli Lilly)

Funding

NSF
Dow
Eli Lilly

Landis Group