Name: _Answer Key_____

CHEM 633: Advanced Organic Chem: Physical
Problem Set 5
Due Thurs, Nov 10, 2016

Please do not look up references until after you turn in the problem set unless otherwise noted. For the following problems, please use Excel (or another graphing program), when necessary. Please submit your graphs with your problem set.

1. (a) Please propose a catalytic cycle for the following reaction (Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1996**, *35*, 200). You may start your catalytic cycle with Pd(PHOX)(dba).
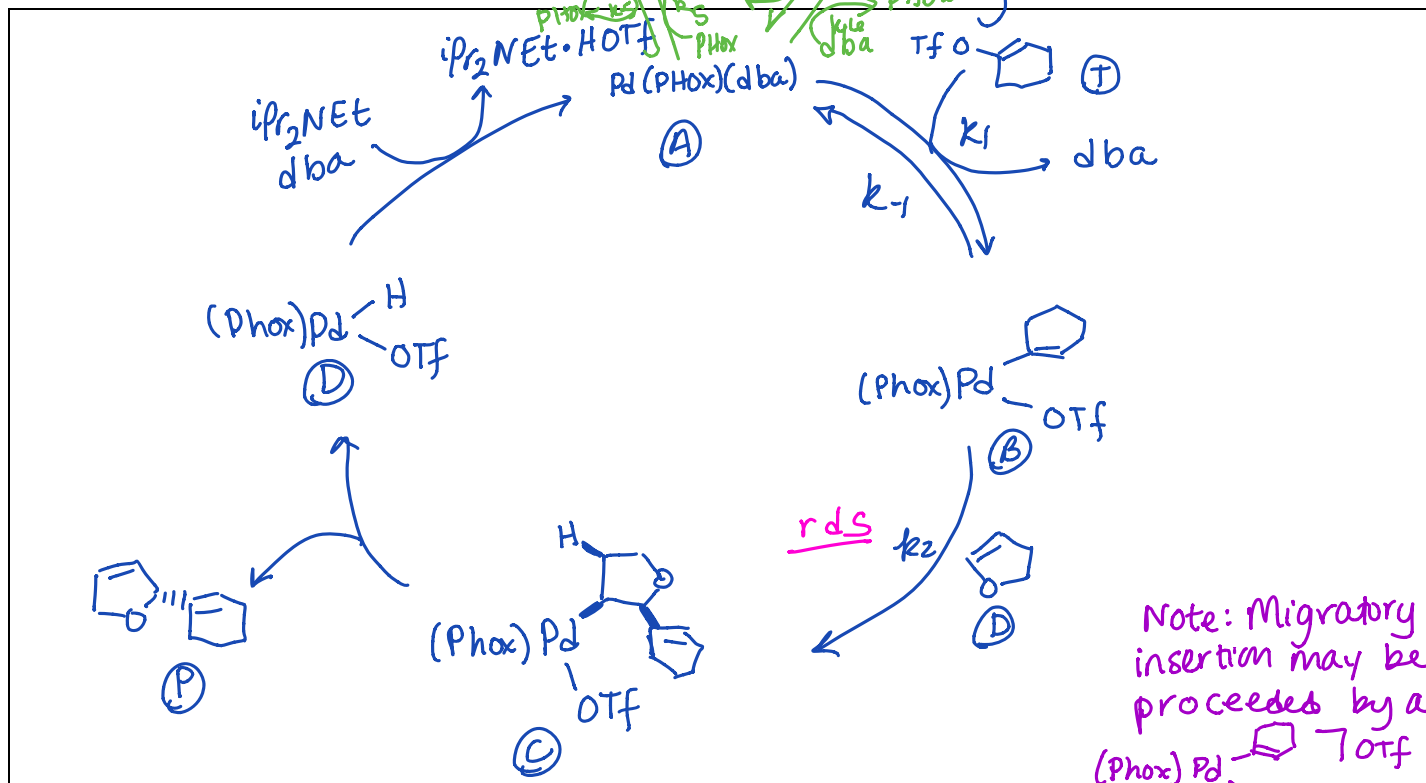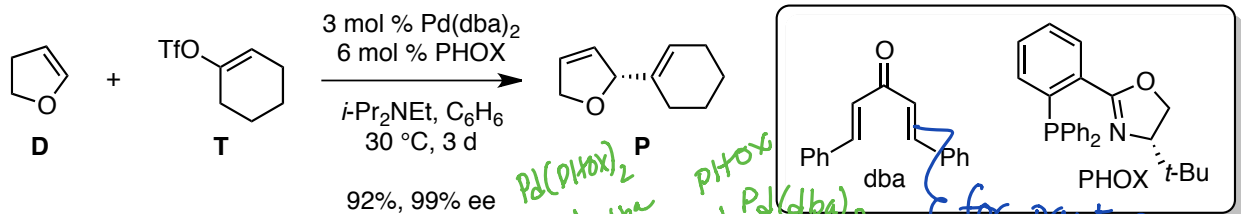
(b) Which named reaction is this?

Heck reaction

This means C & D are **not** catalyst resting states.

(1– continued)

(c) Assuming that migratory insertion is rate-limiting and <u>all subsequent steps to regenerate Pd(PHOX)(dba) are rapid and irreversible</u>, write a "one plus" catalytic rate expression. Use the rate constants you depicted in your catalytic cycle above, and assume that any steps prior to the rate-limiting step are rapid and reversible compared with the rate-limiting step (ie, use the equilibrium approximation). Express you rate law in terms of **D**, **T**, dba and [Pd]$_{total}$.

$$ rate = \frac{\dfrac{k_1 k_2 [Pd]_{total} [D][T]}{k_{-1}[dba]}}{1 + \dfrac{k_1 [T]}{k_{-1}[dba]}} $$

{ everything needs to make product

{ everything that destroys Ⓑ

{ makes Ⓑ

{ destroys Ⓑ

represents Pd (Phox)(dba) Ⓐ

represents Ⓑ

(d) Assuming that migratory insertion is rate-limiting and all subsequent steps to regenerate Pd(PHOX)(dba) are rapid and irreversible, apply the steady-state approximation and derive a "one plus" catalytic rate law for the reaction in terms of **D**, **T**, dba and [Pd]$_{total}$.

$$ rate = \frac{\dfrac{k_1 k_2 [Pd]_{total} [D][T]}{k_{-1}[dba] + k_2 [D]}}{1 + \dfrac{k_1 [T]}{k_{-1}[dba] + k_2 [D]}} $$

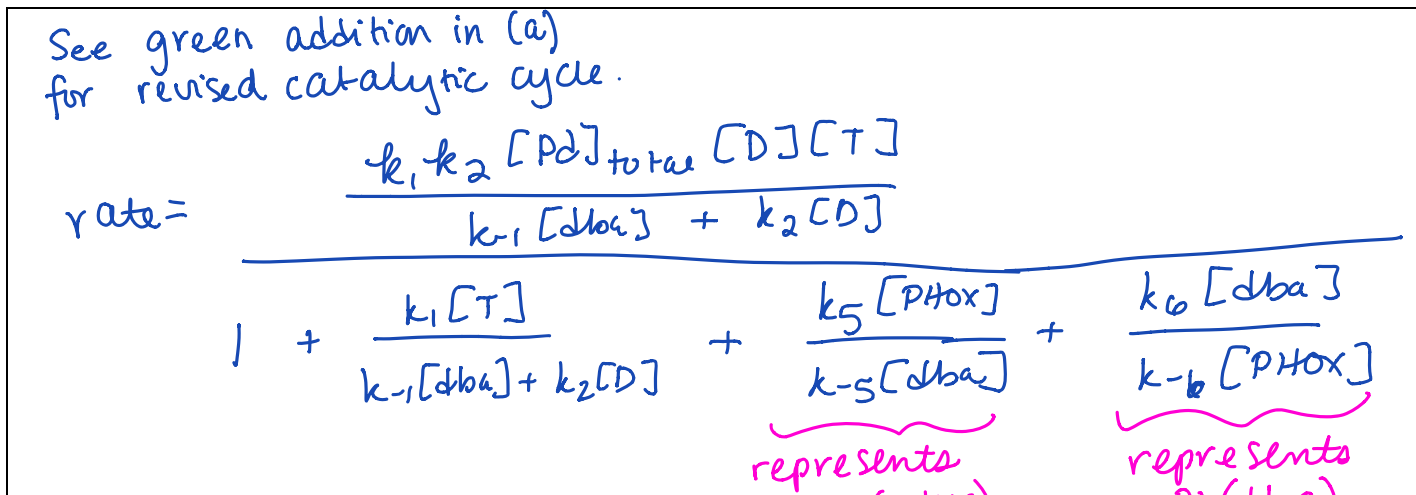(d) Show that your two rate laws are equivalent when k_2 is small compared with k_{-1}.

If $k_2 << k_{-1}$, then $k_{-1}[dba] >> k_2 [D]$ ...

(d) $$ rate = \frac{\dfrac{k_1 k_2 [Pd]_{total} [D][T]}{k_{-1}[dba] + \cancel{k_2 [D]}}}{1 + \dfrac{k_1 [T]}{k_{-1}[dba] + \cancel{k_2 [D]}}} $$

} Same as in (c)

2

(1 – continued)

(e) The dba and PHOX ligand in solution may drag Pd off the catalytic cycle to form Pd(dba)$_2$ or Pd(PHOX)$_2$. Revise your catalytic cycle to include these species. Also revise your "one plus" catalytic rate law to include terms for these species.

See green addition in (a) for revised catalytic cycle.

$$\text{rate} = \cfrac{\cfrac{k_1 k_2 [Pd]_{total}[D][T]}{k_{-1}[dba] + k_2[D]}}{1 + \cfrac{k_1[T]}{k_{-1}[dba] + k_2[D]} + \cfrac{k_5[PHOX]}{k_{-5}[dba]} + \cfrac{k_6[dba]}{k_{-6}[PHOX]}}$$

represents Pd(PHOX)$_2$ as cat. resting state

represents Pd(dba)$_2$
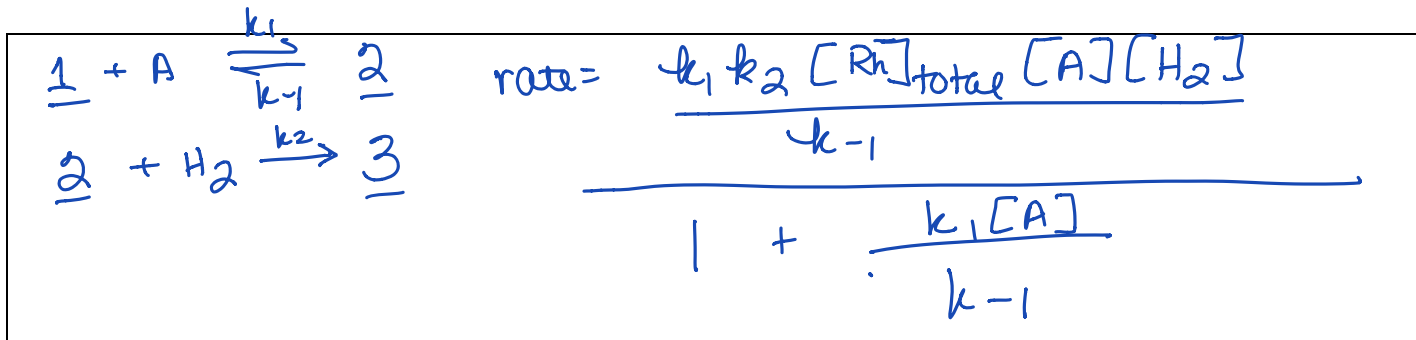
2. The Rh(I)-catalyzed hydrogenation of methyl-(Z)-acetamidocinnamate (A) has been studied. The catalytic cycle shown below has been proposed.

For the math, see attached pages.
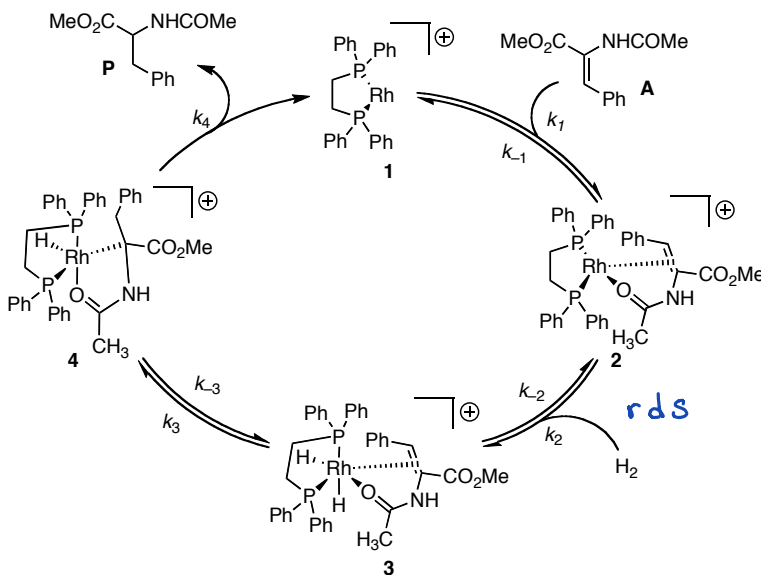
(a) Assuming that the second step (2 –> 3) is rate-limiting and all subsequent steps to regenerate 1 are rapid and irreversible, write down a "one plus" catalytic rate expression. Use the rate constants depicted in the catalytic cycle above, and assume that any steps prior to the rate-limiting step are rapid and reversible compared with the rate-limiting step. (ie, use the equilibrium approximation). Express your rate law in terms of A, H$_2$, and [Rh]$_{total}$.

$$1 + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2$$

$$2 + H_2 \xrightarrow{k_2} 3$$

$$\text{rate} = \cfrac{\cfrac{k_1 k_2 [Rh]_{total}[A][H_2]}{k_{-1}}}{1 + \cfrac{k_1[A]}{k_{-1}}}$$

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(2 – continued)

(b) Assuming that the second step (**2** –> **3**) is rate-limiting and all subsequent steps to regenerate **1** are rapid and irreversible, apply the steady-state approximation to **2** and derive a rate law for the reaction in terms of **A**, H$_2$, and [Rh]$_{total}$.

$$\text{rate} = \cfrac{\cfrac{k_1 k_2 [Rh]_{total} [A][H_2]}{k_{-1} + k_2 [H_2]}}{1 + \cfrac{k_1 [A]}{k_{-1} + k_2 [H_2]}}$$

(c) Show that the equations derived in (a) and (b) are equivalent when k_2 is small compared with k_{-1}.

When $k_2 \ll k_{-1}$ ... $k_2[H_2] \ll k_{-1}$

$$(b): \text{rate} = \cfrac{\cfrac{k_1 k_2 [Rh]_{total} [A][H_2]}{k_{-1} + k_2 [H_2]}}{1 + \cfrac{k_1 [A]}{k_{-1} + k_2 [H_2]}} \quad \left\} \begin{array}{l} \text{Same as} \\ (a). \end{array}\right.$$

(d) The asymmetric hydrogenation of **A** using a chiral diphosphine ligand has an analogous mechanism. Draw a *pair* of catalytic cycles that accounts for the formation of both enantiomers. You may depict the chiral diphosphine generically.

4
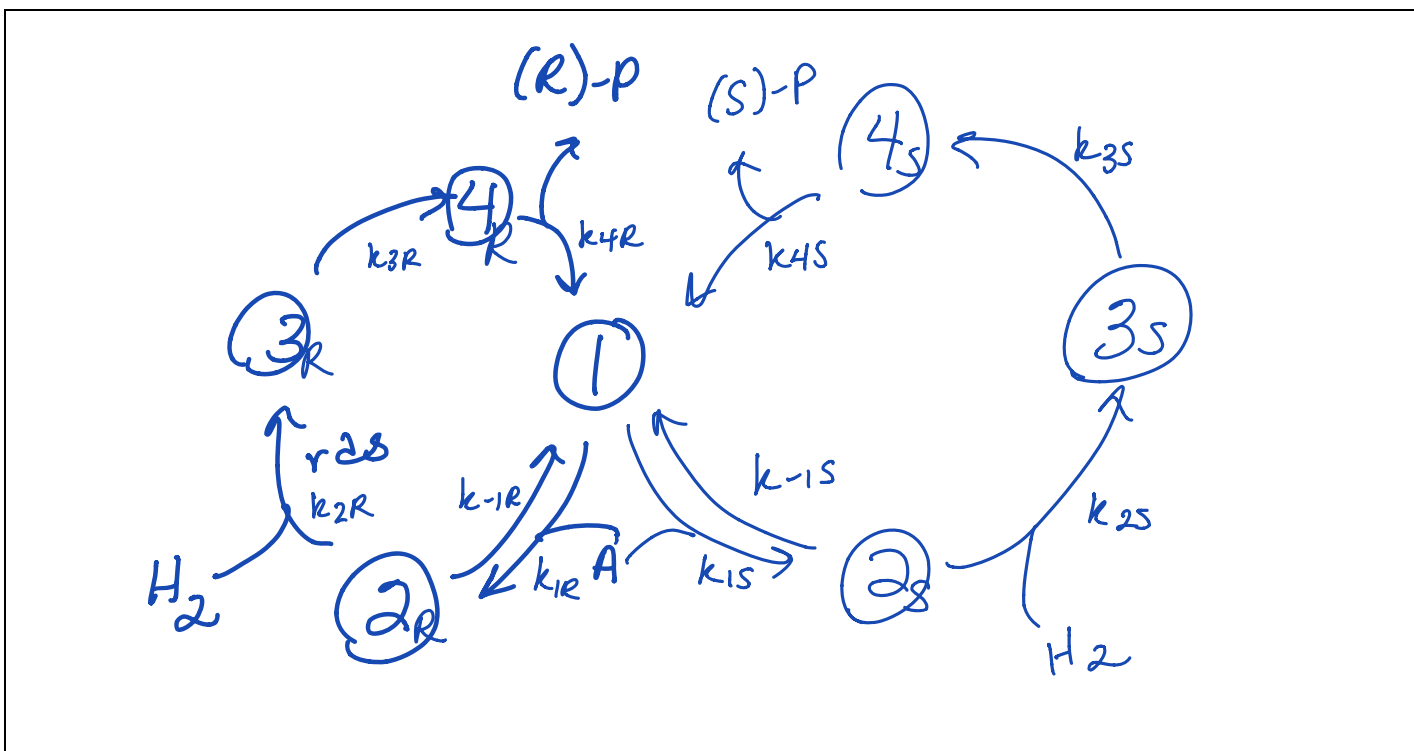
(2 – continued)

(e) With chiral diphosphine ligand: Assuming that the second step (**2** –> **3**) is rate-limiting and all subsequent steps to regenerate **1** are rapid an irreversible, write down a rate law for the total reaction rate using the steady-state approximation. (Hint: Use your "1+" rate law for the non-asymmetric reaction as a basis; it is not necessary to provide a new derivation for this rate law.)

$$\text{rate}_R = \cfrac{\cfrac{k_{1R}\, k_{2R}\, [Rh]_{total}\, [A][H_2]}{k_{-1R} + k_{2R}[H_2]}}{1 + \cfrac{k_{1R}[A]}{k_{-1R} + k_{2R}[H_2]} + \cfrac{k_{1S}[A]}{k_{-1S} + k_{2S}[H_2]}}$$

rate$_{total}$ = rate$_R$ + rate$_S$

$$\text{rate}_S = \cfrac{\cfrac{k_{1S}\, k_{2S}\, [Rh]_{total}\, [A][H_2]}{k_{-1S} + k_{2S}[H_2]}}{1 + \cfrac{k_{1S}[A]}{k_{-1S} + k_{2S}[H_2]} + \cfrac{k_{1R}[A]}{k_{-1R} + k_{2R}[H_2]}}$$

(f) With chiral diphosphine ligand: Show that the relative rates of formation of the two enantiomers depends only on [H_2].

$$\text{relative rates} = \frac{\text{rate}_R}{\text{rate}_S} = \cfrac{\cfrac{\cancel{k_{1R}\, k_{2R}\, [Rh]_{total}\, [A][H_2]}}{k_{-1R} + k_{2R}[H_2]}}{\cancel{1 + \cfrac{k_{1R}[A]}{k_{-1R} + k_{2R}[H_2]} + \cfrac{k_{1S}[A]}{k_{-1S} + k_{2S}[H_2]}}} \cdot \cfrac{\cancel{1 + \cfrac{k_{1S}[A]}{k_{-1S} + k_{2S}[H_2]} + \cfrac{k_{1R}[A]}{k_{-1R} + k_{2R}[H_2]}}}{\cfrac{\cancel{k_{1S}\, k_{2S}\, [Rh]_{total}\, [A][H_2]}}{k_{-1S} + k_{2S}[H_2]}}$$

(g) With chiral diphosphine ligand: Use the boxed experimental data to determine the enantiomeric ratio expected from a reaction run at infinitely low [H_2].

For **R**-enantiomer pathway:
$k_1 = 1.06 \times 10^4\ M^{-1}s^{-1}$
$k_{-1} = 3.2\ s^{-1}$
$k_2 = 630\ M^{-1}s^{-1}$

For **S**-enantiomer pathway:
$k_1 = 5.3 \times 10^3\ M^{-1}s^{-1}$
$k_{-1} = 0.15\ s^{-1}$
$k_2 = 1.1\ M^{-1}s^{-1}$

$$\frac{\text{rate}_R}{\text{rate}_S} = \frac{k_{1R}\, k_{2R}\, (k_{-1S} + k_{2S}[H_2])}{(k_{-1R} + k_{2R}[H_2]) \cdot k_{1S}\, k_{2S}}$$

$$er = \frac{rate_R}{rate_S} = \frac{k_{1R}\, k_{2R}\left(k_{-1S} + k_{2S}[H_2]\right)}{k_{1S}\, k_{2S}\left(k_{-1R} + k_{2R}[H_2]\right)}$$

@ infinitely low $[H_2]$, $k_{-1S} \gg k_{2S}[H_2]$ & $k_{-1R} \gg k_{2R}[H_2]$

$$er = \frac{rate_R}{rate_S} = \frac{k_{1R}\, k_{2R}\, k_{-1S}}{k_{1S}\, k_{2S}\, k_{-1R}} = \frac{(1.06\times10^4\,M^{-1}s^{-1})(630\,M^{-1}s^{-1})(0.15\,s^{-1})}{(5.3\times10^3\,M^{-1}s^{-1})(1.1\,M^{-1}s^{-1})(3.2\,s^{-1})}$$

$$er = 53.7$$

(h) With chiral diphosphine ligand: Use the experimental data from (g) to determine the enantiomeric ratio expected from a reaction run at infinitely high [H₂].

@ infinitely high $[H_2]$, $k_{2S}[H_2] \gg k_{-1S}$ & $k_{2R}[H_2] \gg k_{-1R}$

$$er = \frac{k_{1R}\, k_{2R}\, k_{2S}[H_2]}{k_{1S}\, k_{2S}\, k_{2R}[H_2]} = \frac{(1.06\times10^4\,M^{-1}s^{-1})(3.2\,s^{-1})(1.1\,M^{-1}s^{-1})}{(5.3\times10^3\,M^{-1}s^{-1})(0.15\,s^{-1})(630\,M^{-1}s^{-1})}$$

$$er = 2$$

(i) With chiral diphosphine ligand: Explain why it is necessary to use the steady-state approximation (rather than the pre-equilibrium approximation) to account for the kinetic profile of this reaction.

Pre-equilibrium neglects $k_2[H_2]$ in denominator → assumes $k_{-1} \gg k_2[H_2]$.

Here k_{-1} & $k_2[H_2]$ are too close for this to be a reasonable assumption.

7.

The Rh(I)-catalyzed hydrogenation of methyl-(Z)-acetamidocinnamate (**A**) has been studied. The catalytic cycle shown below has been proposed.
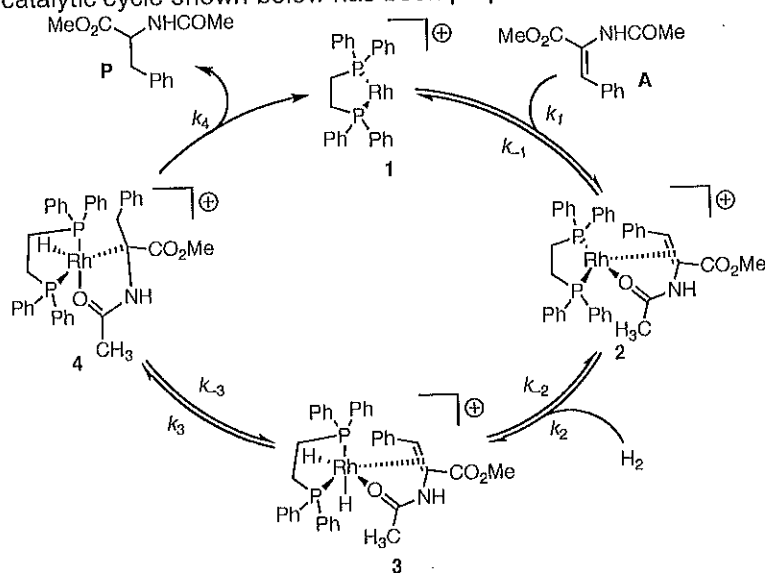
(a) Assuming that the second step (**2 -> 3**) is rate-limiting and all subsequent steps to regenerate **1** are rapid and irreversible, write down a simplified "one plus" catalytic rate expression. Use the rate constants depicted in the catalytic cycle above, and assume that any steps prior to the rate-limiting step are rapid and reversible compared with the rate-limiting step. (ie, use the pre-equilibrium approximation). Express your rate law in terms of **A**, H_2, and $[Rh]_{total}$.

$$C_1 = \frac{k_1}{k_{-1}}$$

$$\text{rate} = \frac{k_2 \, C_1 \, [Rh]_{tot} \, [A][H_2]}{1 + C_1[A]}$$

$$\text{rate} = \frac{\left(\frac{k_1 \, k_2}{k_{-1}}\right) [Rh]_{tot} [A][H_2]}{1 + \frac{k_1}{k_{-1}}[A]}$$

(b) Assuming that the second step (2 -> 3) is rate-limiting and all subsequent steps to regenerate **1** are rapid and irreversible, apply the steady-state approximation to **2** and derive a rate law for the reaction in terms of **A**, H_2, and $[Rh]_{total}$.

$$rate = k_2[H_2][2]$$

$$SSA: \frac{d[2]}{dt} = \emptyset = k_1[1][A] - k_{-1}[2] - k_2[2][H_2]$$

$$[2] = \frac{k_1[1][A]}{k_{-1} + k_2[H_2]} \qquad\qquad [Rh]_{tot} = [1] + [2]$$

$$[1] = [Rh]_{tot} - [2]$$

$$rate = \frac{k_1 k_2 [H_2][1][A]}{k_{-1} + k_2[H_2]}$$

$$k_2[H_2][2] = \frac{k_1 k_2 [H_2][A] \left([Rh]_{tot} - [2]\right)}{(k_{-1} + k_2[H_2])}$$

$$k_2[H_2][2] = \frac{k_1 k_2 [H_2][A][Rh]_{tot}}{(k_{-1} + k_2[H_2])} - \frac{k_1 k_2 [H_2][A][2]}{(k_{-1} + k_2[H_2])}$$

$$k_2[H_2][2] + \frac{k_1 k_2 [H_2][A][2]}{k_{-1} + k_2[H_2]} = \frac{k_1 k_2 [H_2][A][Rh]_{tot}}{(k_{-1} + k_2[H_2])}$$

$$k_2[H_2][2] \left(1 + \frac{k_1[A]}{k_{-1} + k_2[H_2]}\right) = \frac{k_1 k_2 [H_2][A][Rh]_{tot}}{(k_{-1} + k_2[H_2])}$$

$$[2] = \frac{\dfrac{k_1[A][Rh]_{tot}}{(k_{-1} + k_2[H_2])}}{\left(1 + \dfrac{k_1[A]}{k_{-1} + k_2[H_2]}\right)}$$

$$rate = \frac{\dfrac{k_1 k_2 [A][Rh]_{tot}[H_2]}{(k_{-1} + k_2[H_2])}}{\left(1 + \dfrac{k_1[A]}{k_{-1} + k_2[H_2]}\right)}$$

( ) Show that the equations derived in (b) and (c) are equivalent when k_2 is small compared with k_{-1}.

(c) $rate = \dfrac{\dfrac{k_1 k_2 [A][Rh]_{tot}[H_2]}{k_{-1} + k_2[H_2]}}{\left(1 + \dfrac{k_1[A]}{k_{-1} + k_2[H_2]}\right)}$

$k_2[H_2] \ll k_{-1}$, so

$rate = \dfrac{\dfrac{k_1 k_2 [A][Rh]_{tot}[H_2]}{k_{-1}}}{1 + \dfrac{k_1[A]}{k_{-1}}}$

$\Rightarrow$ same as in (b).

(d) The asymmetric hydrogenation of **A** using a chiral diphosphine ligand has an analogous mechanism. Draw a *set* of catalytic cycles that accounts for the formation of both enantiomers. You may depict the chiral diphosphine generically.
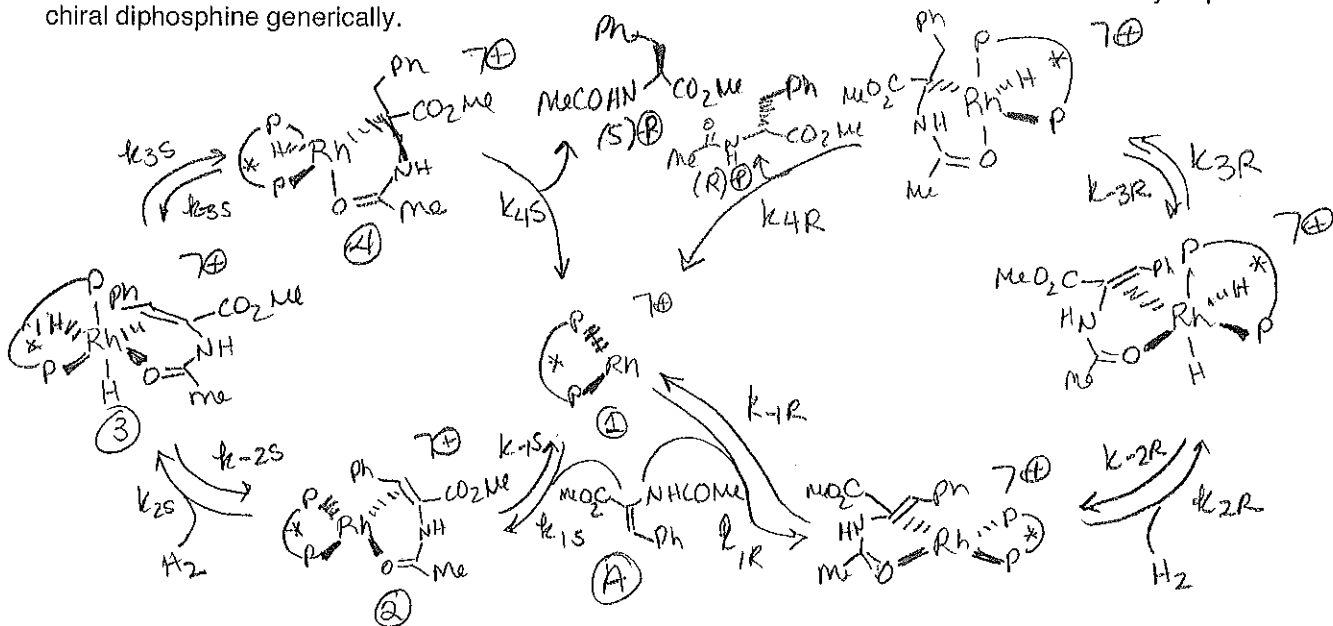
(e)   Assuming that the second step (2 -> 3) is rate-limiting and all subsequent steps to regenerate **1** are rapid an irreversible, write down a rate law for the total reaction rate using the steady-state approximation. (Hint: Use your "1+' rate law for the non-asymmetric reaction as a basis; it is not necessary to provide a new derivation for this rate law.)

Now $[Rh]_{tot} = [1] + [2-S] + [2-R]$

$$rate_R = \cfrac{\cfrac{k_{1R}k_{2R}[A][Rh]_{tot}[H_2]}{(k_{-1R}+k_{2R}[H_2])}}{1 + \cfrac{k_{1R}[A]}{k_{-1R}+k_{2R}[H_2]} + \cfrac{k_{1S}[A]}{k_{-1S}+k_{2S}[H_2]}}$$

$$rate_S = \cfrac{\cfrac{k_{1S}k_{2S}[A][Rh]_{tot}[H_2]}{(k_{-1S}+k_{2S}[H_2])}}{1 + \cfrac{k_{1R}[A]}{k_{-1R}+k_{2R}[H_2]} + \cfrac{k_{1S}[A]}{k_{-1S}+k_{2S}[H_2]}}$$

overall rate = $rate_R$ + $rate_S$

$$rate = \cfrac{[A][Rh]_{tot}[H_2]}{\left(1 + \cfrac{k_{1R}[A]}{k_{-1R}+k_{2R}[H_2]} + \cfrac{k_{1S}[A]}{k_{-1S}+k_{2S}[H_2]}\right)}\left(\cfrac{k_{1R}k_{2R}}{k_{-1R}+k_{2R}[H_2]} + \cfrac{k_{1S}k_{2S}}{k_{-1S}+k_{2S}[H_2]}\right)$$

(f) Show that the relative rates of formation of the two enantiomers depends only on [H$_2$].

$$\frac{rate_R}{rate_S} = \cfrac{\cfrac{k_{1R}\,k_{2R}\,[A][Rh]_{tot}[H_2]}{(k_{-1R}+k_{2R}[H_2])}}{1+\cfrac{k_{1R}[A]}{k_{-1R}+k_{2R}[H_2]}+\cfrac{k_{1S}[A]}{k_{-1S}+k_{2S}[H_2]}}$$

$$\cfrac{\cfrac{k_{1S}\,k_{2S}\,[A][Rh]_{tot}[H_2]}{(k_{-1S}+k_{2S}[H_2])}}{1+\cfrac{k_{1R}[A]}{k_{-1R}+k_{2R}[H_2]}+\cfrac{k_{1S}[A]}{k_{-1S}+k_{2S}[H_2]}}$$

$$\frac{rate_R}{rate_S}=\frac{k_{1R}\,k_{2R}}{k_{1S}\,k_{2S}}\left(\frac{k_{-1S}+k_{2S}[H_2]}{k_{-1R}+k_{2R}[H_2]}\right)$$

(No dependence on [A] or [Rh]$_{tot}$.)

(g) Use the boxed experimental data to determine the enantiomeric ratio expected from a reaction run at infinitely low [H₂].

$$k_{-1S} \gg k_{2S}[H_2]$$

$$k_{-1R} \gg k_{2R}[H_2]$$

$$er = \frac{rate_R}{rate_S} = \frac{k_{1R}\,k_{2R}}{k_{1S}\,k_{2S}}\left(\frac{k_{-1S}}{k_{-1R}}\right)$$

For R-enantiomer pathway:
$k_1 = 1.06 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$
$k_{-1} = 3.2 \text{ s}^{-1}$
$k_2 = 630 \text{ M}^{-1}\text{s}^{-1}$

For S-enantiomer pathway:
$k_1 = 5.3 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$
$k_{-1} = 0.15 \text{ s}^{-1}$
$k_2 = 1.1 \text{ M}^{-1}\text{s}^{-1}$

$$er = \frac{(1.06\times10^4\,\text{M}^{-1}\text{s}^{-1})(630\,\text{M}^{-1}\text{s}^{-1})(0.15\,\text{s}^{-1})}{(5.3\times10^3\,\text{M}^{-1}\text{s}^{-1})(1.1\,\text{M}^{-1}\text{s}^{-1})(3.2\,\text{s}^{-1})}$$

$$\boxed{er = 53.7}$$

(h) Use the experimental data to determine the enantiomeric ratio expected from a reaction run at infinitely high [H₂].

$$k_{-1S} \ll k_{2S}[H_2]$$

$$k_{-1R} \ll k_{2R}[H_2]$$

$$\frac{rate_R}{rate_S} = \frac{k_{1R}\,k_{2R}}{k_{1S}\,k_{2S}}\left(\frac{k_{2S}[H_2]}{k_{2R}[H_2]}\right)$$

$$er = \frac{(1.06\times10^4\,\text{M}^{-1}\text{s}^{-1})(630\,\text{M}^{-1}\text{s}^{-1})(1.1\,\text{M}^{-1}\text{s}^{-1})}{(5.3\times10^3\,\text{M}^{-1}\text{s}^{-1})(1.1\,\text{M}^{-1}\text{s}^{-1})(630\,\text{M}^{-1}\text{s}^{-1})}$$

$$\boxed{er = 2}$$

(i) Explain why it is necessary to use the steady-state approximation (rather than the pre-equilibrium approximation) to account for the kinetic profile of this reaction.

Pre-equilibrium neglects $k_2[H_2]$ term in denominator.

Relative rates are too close of step 1 (k_1 & k_{-1}) and step 2 (k_2)