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**
(c) Assuming that migratory insertion is rate-limiting and all subsequent steps to regenerate \( \text{Pd(PHOX)(dba)} \) are rapid and irreversible, 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 your rate law in terms of \( D, T, \text{dba} \) and \([\text{Pd}]_{\text{total}}\).

\[
\text{rate} = \frac{k_1 k_2 [\text{Pd}]_{\text{total}} [D][T]}{k_1 [\text{dba}]} \]

\[
\text{rate} = 1 + \frac{k_1 [T]}{k_1 [\text{dba}]} \]

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

\[
\text{rate} = \frac{k_1 - k_2 [\text{Pd}]_{\text{total}} [D][T]}{k_1 [\text{dba}] + k_2 [D]} \]

\[
\text{rate} = 1 + \frac{k_1 [T]}{k_1 [\text{dba}] + k_2 [D]} \]

(d) Show that your two rate laws are equivalent when \( k_2 \) is small compared with \( k_1 \).

\[
\text{if } k_2 \ll k_1, \text{ then } [\text{dba}] \gg k_2 [D] \]

\[
\text{rate} = \frac{k_1 k_2 [\text{Pd}]_{\text{total}} [D][T]}{k_1 [\text{dba}] + k_2 [D]} \]

\[
\text{same as in (c)} \]
(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.

\[
\text{rate} = \frac{k_1 k_2 [\text{Pd}]_{\text{total}} [\text{CD}]_T}{k_{-1} [\text{dba}] + k_2 [\text{CD}]_T}
\]

1. \( \text{rate} = \frac{k_1 [\text{CT}]}{k_{-1} [\text{dba}] + k_2 [\text{CD}]_T} + \frac{k_5 [\text{PHOX}]}{k_{-5} [\text{db}] + k_4 [\text{DBA}]} + \frac{k_6 [\text{DBA}]}{k_{-6} [\text{PHOX}]}
\]

represents \( \text{Pd(PHOX)}_2 \)
as cat. resting state

represents \( \text{Pd(dba)}_2 \)

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]$_{\text{total}}$.

\[
\text{rate} = \frac{k_1 k_2 [\text{Rh}]_{\text{total}} [\text{A}] [\text{H}_2]}{k_{-1} [\text{A}]}
\]
(2 – continued)
(b) Assuming that the second step \((2 \rightarrow 3)\) 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 \([\text{Rh}]_{\text{total}}\).

\[
\text{rate} = \frac{k_1 k_2 [\text{Rh}]_{\text{total}} [A][H_2]}{k_1 [A] + k_2 [H_2]} \quad \left(\frac{1}{k_1 + k_2 [H_2]}\right) \quad \left(\frac{k_1 [A]}{k_1 + k_2 [H_2]}\right)
\]

(c) Show that the equations derived in (a) and (b) are equivalent when \(k_2\) is small compared with \(k_1\).

\[
\text{When } k_2 \ll k_1 \Rightarrow k_2 [H_2] \ll k_1 - 1
\]

\[
\text{(b): rate} = \frac{k_1 k_2 [\text{Rh}]_{\text{total}} [A][H_2]}{k_1 + k_2 [H_2]} \quad \left(\frac{1}{k_1 + k_2 [H_2]}\right) \quad \left(\frac{k_1 [A]}{k_1 + k_2 [H_2]}\right)
\]

(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.
(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 and 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.)

$$rate_R = \frac{k_{1R} [Rh]_{total} [A][H_2]}{k_{-1R} + k_{2R}[H_2]} \left( 1 + \frac{k_{1R}[A]}{k_{-1R} + k_{2R}[H_2]} + \frac{k_{1S}[A]}{k_{-1S} + k_{2S}[H_2]} \right)$$

$$rate_S = \frac{k_{1S} [Rh]_{total} [A][H_2]}{k_{-1S} + k_{2S}[H_2]} \left( 1 + \frac{k_{1R}[A]}{k_{-1R} + k_{2R}[H_2]} + \frac{k_{1S}[A]}{k_{-1S} + k_{2S}[H_2]} \right)$$

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

$$relative\ rate = \frac{rate_R}{rates} = \left( \frac{k_{1R} k_{2R} [Rh]_{total} [A][H_2]}{k_{-1R} + k_{2R}[H_2]} \right) \left( 1 + \frac{k_{1R}[A]}{k_{-1R} + k_{2R}[H_2]} + \frac{k_{1S}[A]}{k_{-1S} + k_{2S}[H_2]} \right)$$

(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:**
- $k_1 = 1.06 \times 10^4 \text{ M}^{-1} \text{s}^{-1}$
- $k_{-1} = 3.2 \text{ s}^{-1}$
- $k_2 = 630 \text{ M}^{-1} \text{s}^{-1}$

**For S-enantiomer pathway:**
- $k_1 = 5.3 \times 10^3 \text{ M}^{-1} \text{s}^{-1}$
- $k_{-1} = 0.15 \text{ s}^{-1}$
- $k_2 = 1.1 \text{ M}^{-1} \text{s}^{-1}$
(h) With chiral diphosphi ligand: Use the experimental data from (g) to determine the enantiomeric ratio expected from a reaction run at infinitely high [H₂].

\[
\begin{align*}
\frac{\text{rate}_R}{\text{rate}_S} &= \frac{k_{1R} k_{2R} (k_{-1S} + k_{2S}[H_2])}{k_{1S} k_{2S} (k_{-1R} + k_{2R}[H_2])} \\
\text{at infinitely low} \ [H_2], \ k_{-1S} &\gg k_{2S}[H_2] \quad \& \quad k_{-1R} \gg k_{2R}[H_2] \\
\frac{\text{rate}_R}{\text{rate}_S} &= \frac{k_{1R} k_{2R} k_{-1S}}{k_{1S} k_{2S} k_{-1R}} = \frac{(1.06 \times 10^4 \text{ M}^{-1}\text{s}^{-1})(630 \text{ M}^{-1}\text{s}^{-1})(0.15 \text{s}^{-1})}{(5.3 \times 10^3 \text{ M}^{-1}\text{s}^{-1})(1.1 \text{ M}^{-1}\text{s}^{-1})(3.2 \text{s}^{-1})} \\
\text{er} &= 53.7
\end{align*}
\]

(i) With chiral diphosphi 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 \( \rightarrow \) assume \( k_1 \gg k_2[H_2] \).

Here \( k_1 \) \& \( k_2[H_2] \) are too close for this to be a reasonable assumption.
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. (i.e., use the pre-equilibrium approximation). Express your rate law in terms of A, H₂, and [Rh]_{total}.

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

\[
C_1 = \frac{k_1}{k_{-1}}
\]

\[
\text{rate} = \frac{(k_1k_2/k_{-1}) [\text{Rh}]+[A][H_2]}{1 + \frac{k_1}{k_{-1}} [A]}
\]
(b) Assuming that the second step (2 $\rightarrow$ 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 $[\text{Rh}]_{\text{tot}}$.

\[ \text{rate} = k_2 [H_2] [2^+] \]

\[ \text{SSA: } \frac{d[2^+]}{dt} = \varphi = k_1 [1^-] [A] - k_{-1} [2^-] - k_2 [2^-] [H_2] \]

\[ [2^-] = \frac{k_1 [1^-] [A]}{k_{-1} + k_2 [H_2]} \]

\[ [\text{Rh}]_{\text{tot}} = [1^-] + [2^-] \]

\[ [1^-] = [\text{Rh}]_{\text{tot}} - [2^-] \]

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

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

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

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

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

\[ \text{rate} = \frac{k_1 k_2 [A] [\text{Rh}]_{\text{tot}} [H_2]}{(k_{-1} + k_2 [H_2])} \cdot \left(1 + \frac{k_1 [A]}{k_{-1} + k_2 [H_2]}\right) \]
Show that the equations derived in (b) and (c) are equivalent when $k_2$ is small compared with $k_1$.

(c) \[ \text{rate} = \frac{k_1 k_2 [A][Rh]_\text{tot} [H_2]}{k_1 + k_2 [H_2]} \]

\[ \frac{1}{1 + \frac{k_1 [A]}{k_1 + k_2 [H_2]}} \]

$k_2 [H_2] \ll k_1$, so

\[ \text{rate} = \frac{k_1 k_2 [A][Rh]_\text{tot} [H_2]}{k_1 - 1} \]

\[ \frac{1}{1 + \frac{k_1 [A]}{k_1}} \]

Explain 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 \rightarrow 3) is rate-limiting and all subsequent steps to regenerate 1 are rapid and 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.)

\[
\text{rate}_R = \frac{-k_{lr}[C][CrH_4][CH_2]}{(k_{-1r} + k_{2r}[H_2])}
\]

\[
\text{rate}_S = \frac{-k_{ls}[CA][CrH_4][CH_2]}{(k_{-1s} + k_{2s}[H_2])}
\]

\[
\text{overall rate} = \text{rate}_R + \text{rate}_S
\]

\[
\text{rate} = \frac{[CA][CrH_4][CH_2]}{(1 + \frac{k_{lr}[C]}{k_{-1r} + k_{2r}[H_2]} + \frac{k_{ls}[CA]}{k_{-1s} + k_{2s}[H_2]})} \left( \frac{k_{lr}k_{2r}}{k_{-1r} + k_{2r}[H_2]} + \frac{k_{ls}k_{2s}}{k_{-1s} + k_{2s}[H_2]} \right)
\]
(f) Show that the relative rates of formation of the two enantiomers depends only on $[H_2]$.

\[
\frac{\text{rate}_R}{\text{rates}} = \frac{\frac{k_{1R} k_{2R}[\text{CA}] + [\text{H}_2] + [\text{Rh}]_{\text{tot}}}{(k_{1R} + k_{2R}[\text{H}_2])}}{1 + \frac{k_{1S} [\text{CA}]}{k_{1R} + k_{2R}[\text{H}_2]} + \frac{k_{1S} [\text{CA}]}{k_{1S} + k_{2S}[\text{H}_2]}}
\]

\[
\frac{\text{rate}_R}{\text{rates}} = \frac{k_{1R} k_{2R}}{k_{1S} k_{2S}} \left(\frac{k_{1S} + k_{2S} [\text{H}_2]}{k_{1R} + k_{2R} [\text{H}_2]}\right)
\]

(No dependence on $[\text{CA}]$ or $[\text{Rh}]_{\text{tot}}$.)
(g) Use the boxed experimental data to determine the enantiomeric ratio expected from a reaction run at infinitely low $[H_2]$.

$$k_{-1S} \gg k_{2S} CH_2\text{J}$$
$$k_{-1R} \gg k_{2R} CH_2\text{J}$$

$$\frac{\text{rates}}{\text{rate} R} = \frac{k_{1R} k_{2R}}{k_{1S} k_{2S}} \left( \frac{k_{-1S}}{k_{-1R}} \right)$$

$$\text{er} = \frac{(1.00 \times 10^5 \text{ M}^{-1}\text{s}^{-1})(630 \text{ M}^{-1}\text{s}^{-1})(0.15 \text{s}^{-1})}{(5.3 \times 10^3 \text{ M}^{-1}\text{s}^{-1})(1.1 \text{ M}^{-1}\text{s}^{-1})(3.2 \text{s}^{-1})}$$

$$\text{er} = 53.7$$

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

(h) Use the experimental data to determine the enantiomeric ratio expected from a reaction run at infinitely high $[H_2]$.

$$k_{-1S} \ll k_{2S} CH_2\text{J}$$
$$k_{-1R} \ll k_{2R} CH_2\text{J}$$

$$\frac{\text{rates}}{\text{rate} R} = \frac{k_{1R} k_{2R}}{k_{1S} k_{2S}} \left( \frac{k_{2S} CH_2\text{J}}{k_{2R} CH_2\text{J}} \right)$$

$$\text{er} = \frac{(1.00 \times 10^5 \text{ M}^{-1}\text{s}^{-1})(630 \text{ M}^{-1}\text{s}^{-1})(1.1 \text{ M}^{-1}\text{s}^{-1})}{(5.3 \times 10^3 \text{ M}^{-1}\text{s}^{-1})(1.1 \text{ M}^{-1}\text{s}^{-1})(630 \text{ M}^{-1}\text{s}^{-1})}$$

$$\text{er} = 2$$

(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 ($k_1 \approx k_{-1}$) and step 2 ($k_2$)