Frontiers of Chemistry Seminar

(left) Part 1. Concurrent Tandem Catalysis (CTC)

(right) Part 2. Discussion on the emerging Avian Bird-Flu

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What is Concurrent Tandem Catalysis (CTC)

"...which involves the cooperative action of two or more catalytic cycles in a single reactor."

CTC Classification

(AIB)(BIIIP)

CTC Classification

(AIB)(BCIP)

"CTC constitutes a significant challenge for synthetic chemists and presents a number of opportunities to improve chemical transformation."

- "...could circumvent the time and yield losses associated with isolation and purification..."
- "Generating harmful chemicals in situ, followed by incorporation..."
- "...molecular species that are too unstable for isolation may be transformed into useful products by quickly entering a subsequent catalytic cycle prior to decomposition."
- "...may allow the coupling of equilibrium-limited reactions with subsequent exothermic ones."

What is Concurrent Tandem Catalysis (CTC)

- What constitutes concurrent tandem catalysis...
  
  • "Reactions in which a **single metal species** is added, but is capable of two or more **distinct** chemical transformations involving **discrete** molecular products..."

- What does **NOT** constitute concurrent tandem catalysis...
  
  • "...single-pot tandem catalysis in which **additional reagents are added after** a given cycle is complete..."

  • "...reactions employing a cocatalyst that regenerates the active catalyst...since only one catalyzed reaction involving a substrate takes place." **(No Wacker-type oxidation)**

  • "...domino reactions where multiple transformations of the substrate occur **without discrete metal-free intermediates.**"

Catalytic NHK Reaction: A Borderline Example of CTC

I = CrX₂; II = NiCl₂; C = CrCl₃; G = Mn

"...is a borderline example of CTC, but it was included because it manifests many of the appealing features of transition-metal mediated CTC cycles."

What is Concurrent Tandem Catalysis (CTC)

*Other examples of catalytic schemes...

Two catalysts react with the same substrate

\[(\text{A}_1\text{B})(\text{A}_{II}\text{P})\]

Polymerization of ethylene to branched polyethylene

\[(\text{A}_1\text{B})(\text{AB}_{II}\text{P})\]

(\text{A}_{II}\text{P})

Examples of Concurrent Tandem Catalysis

Examples where a Single Catalyst is Involved in Multiple Catalytic Systems
Stille Couplings Catalytic in Tin: The "Sn–O" Approach

Key Issue: Find a way to recycle \( R_3SnX \) into \( R_3SnH \)

Possible side reactions:
- Dimerization of \( R_3SnH \)
- Reduction of the organohalide

Conditions; Cat. 1 (1 mol%), Me\(_3\)SnCl (6 mol%), Cat. 2 (1 mol%), (2-furyl)\(_3\)P (4 mol%)
aq. Na\(_2\)CO\(_3\), PMHS, Et\(_2\)O, 37 °C, 15 h

Parallel Recognition by Kinetic Control

Conditions; Cat. 1 (10 mol%), diene (1.3 equiv), Sn(allyl)$_4$ (1.2 equiv), CH$_3$CN, 0 °C, 2 h

What makes this result interesting...

- The starting material is prone to redistribution

100:0:0 (without catalyst, 12 h)
50:27:23 (10 mol% catalyst, 1 h)

- Also, the sequential addition of both reagents gives lower yields (scrambling) and is less selective, especially for the allylation

Hexahydro-4H-Chromens by Hydroformylation/Ene Reaction/Hydroformylation/Dehydration

Conditions; Cat. 1 (1 mol%), PPh₃ (3 mol%), dioxane or toluene, CO (50 bar), H₂ (50 bar), 120 °C, 70 h

Silacyclohexanes by Hydroformylation/Aldol/Hydrogenation

\[
\begin{align*}
\text{HN}(R^3)_2 & \xrightarrow{\text{Cat. 1}} \begin{array}{c} \text{R}^1 \text{Si} \text{R}^2 \text{R}^2 \end{array} \xrightarrow{\text{CO}} \begin{array}{c} \text{R}^1 \text{Si} \text{R}^2 \text{R}^2 \end{array} \xrightarrow{\text{Cat. 1}} \begin{array}{c} \text{R}^1 \text{Si} \text{R}^2 \text{R}^2 \end{array} \xrightarrow{\text{Cat. 1}} \begin{array}{c} \text{R}^1 \text{Si} \text{R}^2 \text{R}^2 \end{array} \\
X = \text{OH}, \text{N}(R^3)_2
\end{align*}
\]

\[
\begin{align*}
\text{HN}(R^3)_2 & \xrightarrow{-\text{H}_2\text{O}} \begin{array}{c} \text{R}^1 \text{Si} \text{R}^2 \text{R}^2 \end{array} \xrightarrow{\text{Cat. 1}} \begin{array}{c} \text{R}^1 \text{Si} \text{R}^2 \text{R}^2 \end{array} \xrightarrow{\text{Cat. 1}} \begin{array}{c} \text{R}^1 \text{Si} \text{R}^2 \text{R}^2 \end{array} \\
\text{Cat. 1} & \begin{array}{c} \text{Rh}(\text{acac})(\text{CO})_2 \\
(\text{AB}_2\text{C})(\text{C}_1\text{D})(\text{DE}_2\text{F})\text{FG}\text{H})(\text{EH}_2\text{P})
\end{array}
\end{align*}
\]

Conditions; Cat. 1 (1 mol%), PPh₃ (4 mol%), morpholine (2.7 equiv), CH₂Cl₂, CO (20 bar), H₂ (40 bar), 90 °C, 20-96 h

\[
\begin{align*}
\text{Ph} & \text{Ph} \quad \text{Ph} & \text{Ph} \quad \text{Ph} & \text{Ph} \quad \text{Si} \quad \text{Si} \quad \text{Si} \quad \text{Si} \quad \text{Bu} & \text{Si} & \text{Ph} & \text{Si} \\
95\% & 79\% & 54\% & 92\% & 64\% \text{ de} & 68\% >95\% \text{ de}
\end{align*}
\]

Concurrent Hydroamination/Hydrosilation

\[
\begin{align*}
\text{Cat. 1} & \quad \text{++- BPh}_4 \\
\text{Cat. 1} & \quad \text{++- BPh}_4
\end{align*}
\]

Conditions; Cat. 1 (2 mol%), Et\textsubscript{3}SiH, THF-\textsubscript{d\textsubscript{8}}, 60 °C (reaction monitored by \textsuperscript{1}H NMR)

Amination/Annulation/Aromatization

\[
\begin{align*}
\text{R}^1 \text{R}^2 & \quad \text{H}_2 \text{N} \quad \text{H}_2 \text{O} \\
\text{Cat. 1} & \\
\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O} & \quad \text{2 best catalysts} \\
\text{CuCl}_2 \cdot 2\text{H}_2\text{O} & \\
+ 19 \text{ other catalysts} & \\
\text{Conditions; Cat. 1 (2.5 mol%), EtOH, 78-100 °C, 5-24 h} & \\
\text{R}^1 & = \text{Ph, 74%} \\
\text{R}^1 & = \text{t-Bu, 69%} \\
\text{n} & = 1, 77\% \\
\text{n} & = 4, 67\% \\
\text{R}^1 & = \text{H, 78%} \\
\text{R}^1 & = \text{F, 66%} \\
\text{R}^1 & = \text{Br, 68%} \\
\text{Ph} & \\
\text{70\%} & \\
\text{96\%} & \\
\end{align*}
\]

2,6-Dioxabicyclo[4.3.0]nonenes by ROM/CM/RCM

Conditions; Cat. 1 (8 mol%), CH₂Cl₂, rt, 3 h

Examples of Concurrent Tandem Catalysis

Examples where two Different Catalysts are Involved in Multiple Catalytic Systems
Bicyclopentenones by Allylation/Pauson-Khand Reaction

Conditions: Cat. 1 (1.5 mol%), dppb (3.0 mol%), BSA (1.2 equiv), Cat. 2 (7 mol%), Toluene, CO (1 atm), 110 °C, 35 h

BSA = bis(trimethylsilyl)acetamide

Furanes by Propargylic Substitution/Hydration/Cyclization

\[
\begin{array}{c}
\text{Cat. 1} \\
\text{Cat. 2}
\end{array}
\]

\[
\begin{array}{c}
*\text{Cp} \quad \text{Ru} = \text{Ru} \quad \text{Cp}^* \\
\text{MeS} \quad \text{Cl} \quad \text{Cl} \quad \text{SMe}
\end{array}
\]

\[
\begin{array}{c}
\text{PtCl}_2
\end{array}
\]

Conditions; Cat. 1 (10 mol%), NH₄BF₄ (20 mol%), Cat. 2 (20 mol%), acetone, reflux, 36–72 h

Furanes by Propargylic Substitution/Hydration/Cyclization

Conditions: Cat. 1 (10 mol%), NH₄BF₄ (20 mol%), Cat. 2 (20 mol%), acetone, reflux, 100 h

Acetals by Hydroformylation/Acetalization of Alkenes

\[
\begin{align*}
\text{R}^1 \text{CH} &= \text{R}^1 \text{CHO} \\
\text{Cat. 1} &\quad \text{Cat. 2} \\
\text{[Rh}_2(\mu-\text{OMe})_2(\text{COD})_2] &\quad \text{PPTS} \\
\text{SnCl}_2 \text{ and PTSA not successful} &
\end{align*}
\]

Conditions: Cat. 1 (1 mol%), PPh₃ (10 mol%), Cat. 2 (5 mol%), HC(OEt)_₃, 60 °C, CO/H₂, 50 bar 12-24 h

Formate Decarbonylation/Aryl Halide Alkoxy carbonylation

Cat. 1
Ru₃(CO)₁₂

Cat. 2
\[ \text{all effective} \]
\[ \text{PdCl}_2, \text{Pd(OAc)}₂, \text{Pd(PPh₃)}₄, \text{Pd₂(dba)}₃, \text{Pd/C} \]

Conditions: Cat. 1 (3 mol%), Cat. 2 (2 mol%), NaHCO₃, DMF, 135 °C

R = 4-Me, 4-OMe, 4-OH, 4-COCH₃
2,6-Me₂, 3-Br,

**DKR of Allylic Acetates/Transesterification**

Cat. 1

\[ \text{Pd(PPh}_3\text{)}_4 \]

*Candida antartica lipase B*

(CALB, Novozym 435)

*Pseudomonas cepacia lipase*

Cat. 2

Conditions; Cat. 1 (5 mol%), dppf (15 mol%), \( i \)-PrOH (10 equiv), Cat. 2 (200-400 mg/mmol), THF, rt, 1.5-3 d

\[ \begin{align*}
R^1 = H, & \quad 71\%(98) \\
R^1 = Cl, & \quad 67\%(97) \\
R^1 = Me, & \quad 70\%(98) \\
\end{align*} \]

Chemoenzymatic DKR/Acylation

\[
\begin{align*}
\text{NH}_2 & \quad \xrightarrow{\text{Cat. 1}} \quad \text{NH}_2 \\
\text{R}_1 \text{R}_2 & \quad \xrightarrow{\text{Cat. 2}} \quad \text{NHAc} \\
\text{R}_1 \text{R}_2 & \quad \xrightarrow{\text{Cat. 2}} \quad \text{NHAc}
\end{align*}
\]

Cat. 1

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{OC} & \quad \text{Ru} \cdot \text{Cl} \\
\text{CO} & \quad \text{CO}
\end{align*}
\]

Cat. 2

\[
\begin{align*}
\text{NH}_{i-\text{Pr}} & \\
\text{R} & \quad \text{H} \\
\text{O} & \quad \text{H} \\
\text{O} & \quad \text{O}
\end{align*}
\]

Cat. 2

\[
\begin{align*}
\text{R} & \quad \text{Ph}, \text{p-F-C}_6\text{H}_4, \text{p-OMe-C}_6\text{H}_4 \\
\text{R} & \quad \text{Ph}, \text{p-F-C}_6\text{H}_4, \text{p-OMe-C}_6\text{H}_4
\end{align*}
\]

Candida antartica lipase B (CALB, Novozym 435)

(A,B)(B,A)(A,I,P)

Conditions: Cat. 1 (4 mol%), i-PrOAc, Cat. 2 (40 mg/mmol of amine), Na$_2$CO$_3$, Toluene, 90 °C, 3 d

\[
\begin{align*}
\text{NHAc} & \quad \text{NHAc} \\
\text{NHAc} & \quad \text{NHAc}
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R}
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{NHAc} \\
\text{R} & \quad \text{NHAc} \\
\text{R} & \quad \text{NHAc} \\
\text{R} & \quad \text{NHAc}
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{NHAc} \\
\text{R} & \quad \text{NHAc} \\
\text{R} & \quad \text{NHAc} \\
\text{R} & \quad \text{NHAc}
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{NHAc} \\
\text{R} & \quad \text{NHAc} \\
\text{R} & \quad \text{NHAc} \\
\text{R} & \quad \text{NHAc}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{NHAc} \\
\text{Ph} & \quad \text{NHAc} \\
\text{Ph} & \quad \text{NHAc} \\
\text{Ph} & \quad \text{NHAc}
\end{align*}
\]

\[
\begin{align*}
\text{78%}(95) & \quad \text{85%}(93)
\end{align*}
\]

Cyclic Enol Ethers by RCM/Olefin Isomerization

Conditions; Cat. 1 (10 mol%), CH₂Cl₂, N₂/H₂ (95:5, 1 atm), 45-70 °C, 6-12 h

R¹= H, 61%
R¹ = OMe, 65%
R¹ = Cl, 58%

<10% olefin hydrogenation obtained

Cross-Metathesis/Hydrogenation

\[
\text{Cat. 1} \quad \text{Cat. 2}
\]

\[
\begin{align*}
\text{Mes} & \quad N \quad N \quad \text{Mes} \\
\text{Cl-Ru} & \quad \text{PtO}_2 \\
\end{align*}
\]

Conditions: Cat. 1 (5 mol%), Cat. 2 (5 mol%), CH\textsubscript{2}Cl\textsubscript{2}, H\textsubscript{2} (1 atm), rt, 15 h

**Allylic Acetate Isomerization/Ring-Closing Metathesis**

\[
\text{Pd(PPh}_3)_4 \quad \text{Pd}_2(\text{dba})_3
\]

**Conditions:** Cat. 1 (5 mol%), PPh\textsubscript{3} (20 mol\%), Cat. 2 (5 mol\%), CDCl\textsubscript{3}, rt, 20 h

\[
\begin{align*}
\text{Cat. 1} & \quad \text{Cat. 2} \\
\text{Pd(PPh}_3)_4 & \quad \text{PCy}_3 \\
\text{Pd}_2(\text{dba})_3 & \quad \text{Cl}_2 \text{Ru} = \text{Cl}_2 \text{PCy}_3 \text{Ph}
\end{align*}
\]


Concurrent Tandem Catalysis: Future Prospects

❖ CTC based on artificial systems is in its infancy.

❖ Challenges that need to be overcome...

  • "...a more precise understanding of structure/reactivity relationships at the molecular level should give better guidelines for choosing catalyst partners."

  • "...matching the rates of the individual catalytic cycles."
    
    *Insight into mechanism, ability to control TOF, transferring cycle products within the same medium*

  • "Characterization of active sites in heterogeneous catalysts..."

  • "...multifunctional catalysts that effect different types of transformations under identical reaction conditions should alleviate compatibility concerns."

Discussion on the Emerging Avian Bird-Flu

- What is the Bird Flu?
- What are the available antiviral drugs?
What is Influenza (Flu)?

❖ Occurrence

• "...occurs in annual seasonal epidemics -- in the Northern Hemisphere these are normally between September and February..."

• "...local epidemics are clear cut and normally last for 6-8 weeks."

❖ Transmission

• "...spread via droplets and small particle aerosols which are formed when subjects talk, cough or sneeze..."

• "...enter through the nose or mouth and deposit in the upper and lower respiratory tract to initiate replication."

• "The viral target in humans is the upper respiratory tract epithelial cells."

❖ Clinical illnesses associated with Influenza

• "...sore throat, nasal obstruction, rhinorrhea and sneezing."

• "...complications in the upper respiratory tract such as sinusitis and otitis media."

• "In the lower respiratory tract, an acute bronchitis and pneumonia are well recognised as well as exac- cerbations of pre-existing disease such as asthma and chronic obstructive pulmonary disease (COPD)."

• "Much rarer systemic complications include myositis, myocarditis and encephalitis."

Johnston, L. S. Virus Res. **2002**, 82, 147
Influenza (Flu): The Pandemics of the 20th Century

To most of us, flu is a nuisance disease, an annual hassle...

- According to the World Health Organisation (WHO) 3 to 5 million cases of seasonal influenza occur every year (250 000-500 000 die, mostly the elderly, the very young and those who have underlying respiratory and cardiovascular disease).

Timeline of the pandemics of the 20th Century

- 1900: H1N1
- 1918: Spanish Flu - 50-100 Million deaths
- Bird origin suspected
- Everyone one earth was exposed to the disease, half got sick

- 1957: H2N2
- Asian Flu - 1 Million deaths
- Bird-human viruses mix

- 1968: H3N2

- 1977: H1N1
- Russian Flu (minor pandemic)

- 1997: H5N1 Bird-Flu
- 18 cases, 6 deaths
- Bird-human viruses mix

- 2000: Hong Kong Flu
- 750 000 deaths
- Bird-human viruses mix
Global Incidence of the Human Influenza A (H5N1)

- "The largest number of cases has occurred in Vietnam, particularly during the third, ongoing wave..."
- "...first human death was recently reported in Indonesia..."


- First reported case outside of Asia happened in January in Turkey.

Global Incidence of the Human Influenza A (H5N1)

- "The outbreak has targeted children and adults with the maximum toll in the age group of 10-19 years."


Global Incidence of the Human Influenza A (H5N1)

- "The outbreak has targetted children and adults with the maximum toll in the age group of 10-19 years."


What is Influenza?

"If you know the enemy and know yourself, you need not fear the result of a hundred battles. If you know yourself but not the enemy, for every victory gained you will also suffer a defeat."  

Sun Tzu

Chinese Military Strategist

Somewhere between
500-320 B.C.
What does a Flu Virus Virion look like?

**Glycoproteins**

- HA binds to terminal Sialic acid
- NA cleaves terminal Sialic acid

**Genome**

- 8 separate RNA strands (2 of these synthesize HA and NA)
- Increases the potential for recombinants to form (by interchange of gene segments if two different viruses infect the same cell)

**New Flu Strains**

50-100 NA spikes (10% visible spikes)

Size: 100 nm
Why/How do Pandemics occur?

• Antigenic Variation

  "The plethora of different strains...is primarily related to mutations in the viral genes of two surface glycoproteins, HA and NA."

  "...these mutations arise primarily from incremental changes in the amino acid sequences of these glycoproteins by selection pressure of the immune system of the infected host."

  "...infrequently a mutation arises by genetic re-assortment of viruses from different animal hosts..."

  A bird strain of Influenza A can directly jump to humans
  A virus can jump to an intermediate host (such as a pig) and then to humans
  Genetic mixing, after two flu strains meet in the same cell

  "...an entirely new gene for one of the surface glycoproteins is generated which is significantly different (50%) in amino acid sequence of the parent virus."

  "This is the mechanism by which new subtypes of influenza arise which is primarily responsible for the major pandemics that occur."

Why/How do Pandemics occur?

*Antigenic Shift*

**Influenza A**
- 9 known subtypes of NA (N1 to N9)
- 13 known subtypes of HA (H1 to H13)

**Influenza B**
- 1 known subtype
- Only present in humans

**Influenza C**
- Rare strain
- Only present in humans

*Only 5 subtypes are known to infect humans...most of the other subtypes circulate in birds*

What are the available antiviral drugs?
What are the Available Antiviral Drugs?

Antiviral Drugs

Adamanates

\[
\begin{align*}
\text{NH}_3\text{Cl} & \quad \text{NH}_3\text{Cl} \\
\text{Amantadine} & \quad \text{Rimantadine}
\end{align*}
\]

Interfere with viral uncoating inside the cell

Neuraminidase Inhibitors

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{O} & \quad \text{O} \\
\text{CO}_2\text{H} & \quad \text{CO}_2\text{Et} \\
\text{AcHN} & \quad \text{AcHN} \\
\text{NH}_2 & \quad \text{NH}_2 \quad \text{H}_3\text{PO}_4
\end{align*}
\]

Zanamivir (Relenza)

Oselamivir (Tamiflu)

Cheaper and more readily available

Side-effects (seizures)
Not effective against most Avian Flu strains
Can encourage drug-resistant strains to emerge

Minor side-effects (nausea, vomiting
and abdominal pain)
Development of resistance is very rare

**Figure 1. Mechanism of Action of Neuraminidase Inhibitors.**

Panel A shows the action of neuraminidase in the continued replication of virions in influenza infection. The replication is blocked by neuraminidase inhibitors (Panel B), which prevent virions from being released from the surface of infected cells.
**Tamiflu: First Approach**

Shikimic acid, which comes from a wild variety of the spice star anise, is used as starting material.

Roche has spliced the gene that makes shikimic acid into bacteria.

Tamiflu: Second Approach

Scheme 2. Roche-Basel route to oseltamivir phosphate 1

Azide-free approach

Tamiflu: Third Approach

Scheme 3. Second-generation route to oseltamivir phosphate 1

Tamiflu (Oseltamivir): Treatment against the Bird Flu

- "Tamiflu is proven to be effective in the treatment and for the prevention of influenza in adults and in children 1 year and older."

- "The dose for the adult treatment of influenza is a 75 mg capsule, taken twice daily for five days. One pack of Tamiflu contains a full treatment course of 10 capsules."

- "Treatment must commence within 48 hours of the onset of symptoms for full efficacy. For post exposure prophylaxis the dosage is one 75 mg capsule daily for up to 6 weeks."

- "NEJM confirms importance of Tamiflu as a treatment option and that stockpiling should be part of pandemic-preparedness plans."

- "In August 2005, Roche announced the donation of another 3 million treatment courses of Tamiflu to the WHO for rapid deployment at the epicentre of the pandemic."

- "3 million treatment courses is the quantity indicated by modelling (Science, Nature) that will reduce morbidity and mortality and help delay its spread in an affected nation."