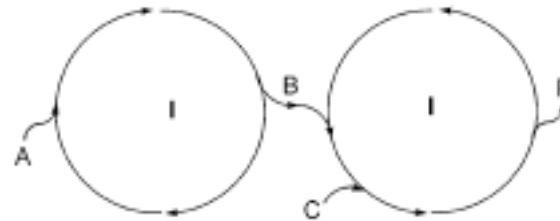
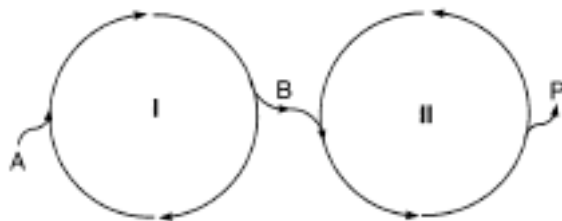


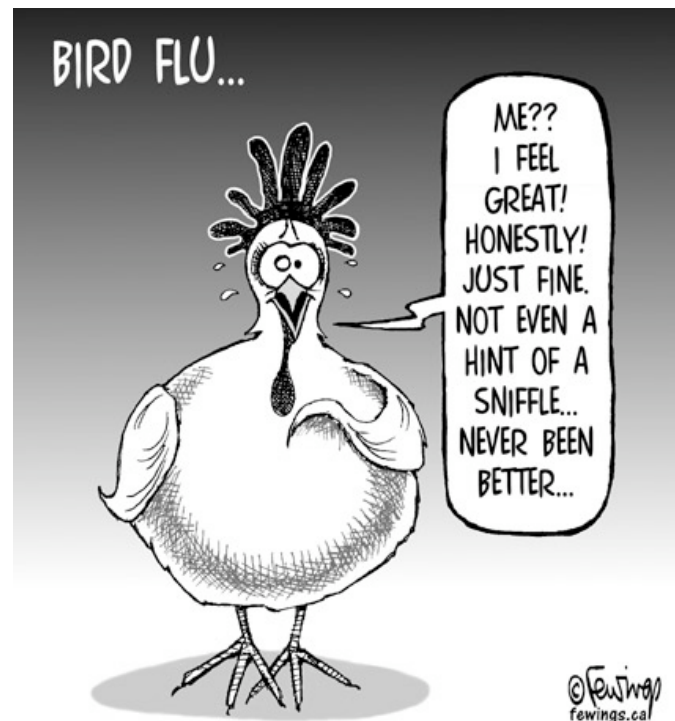
Frontiers of Chemistry Seminar

•→ Part 1. Concurrent Tandem Catalysis (CTC)



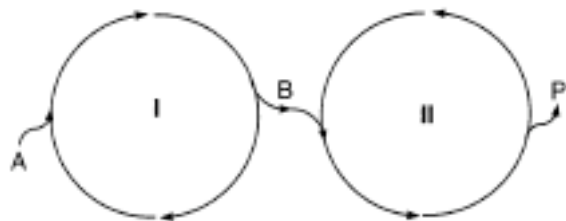
•→ Part 2. Discussion on the emerging Avian Bird-Flu

Michel Grenon, University of Pittsburgh
January 7th, 2006



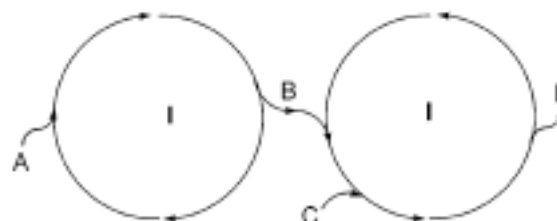
What is Concurrent Tandem Catalysis (CTC)

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



CTC Classification

(A_IB)(B_{II}P)



CTC Classification

(A_IB)(BC_IP)

➔ "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."

Wasike, J.-C.; Obrey, S. J.; Baker, T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001

What is Concurrent Tandem Catalysis (CTC)

➔ What constitutes concurrent tandem catalysis...

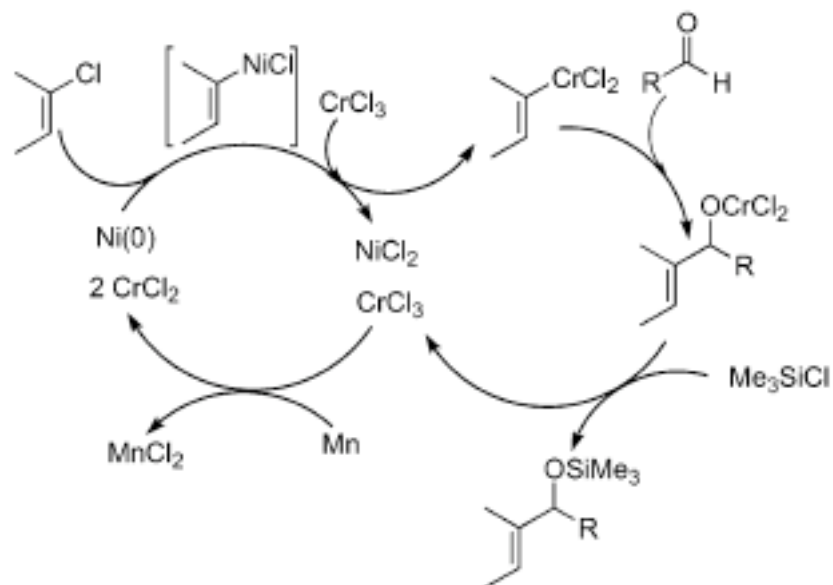
- "Reactions in which a **single metal species** is added, but is capable of two or more **distinct** chemical transformations involving **discrete** molecular products..."

➔ 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.**"

Wasike, J.-C.; Obrey, S. J.; Baker, T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001

Catalytic NHK Reaction: A Borderline Example of CTC



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

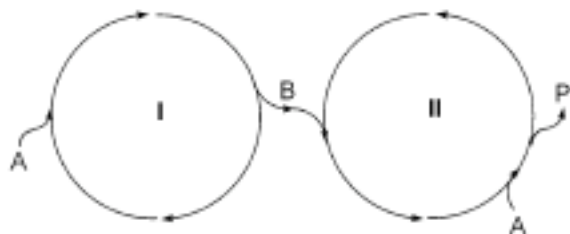
(AI_{II}BC)(BD→E)(EF→PC)(CG→HI)

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

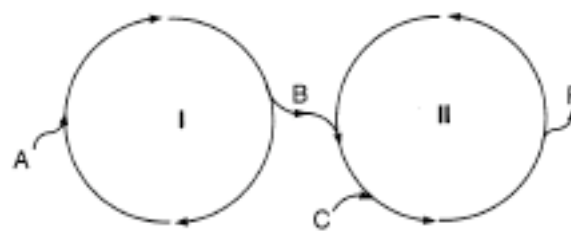
Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2553 and 12349

What is Concurrent Tandem Catalysis (CTC)

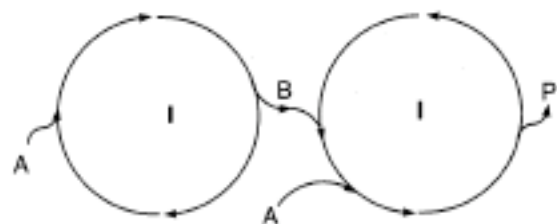
→ Other examples of catalytic schemes...



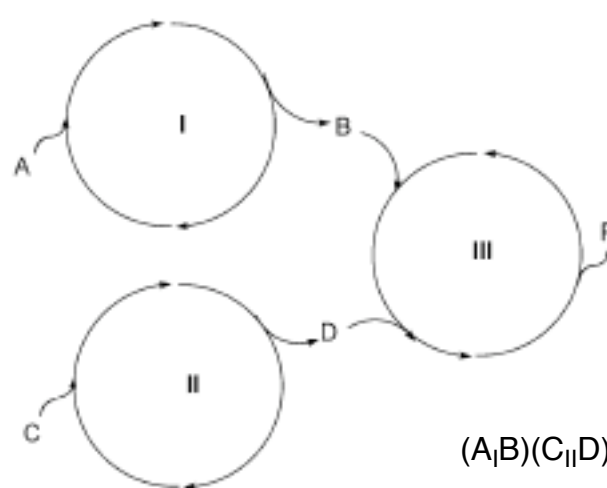
Two catalysts react with the same substrate
(A_IB)(A_{II}P)



(A_IB)(B C_{II}P)



Polymerization of ethylene to branched polyethylene
(A_IB)(A B_IP)



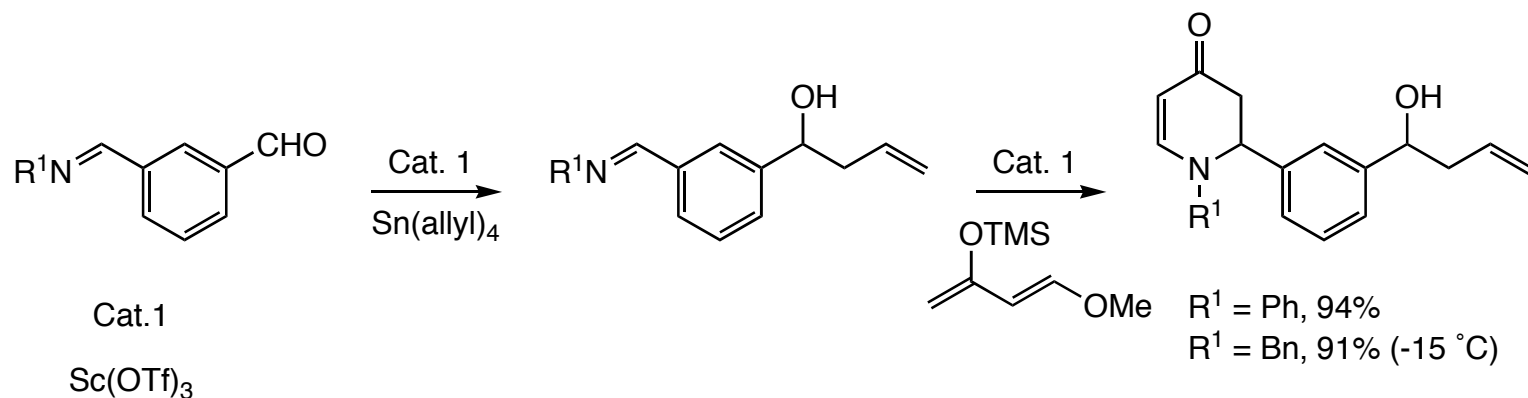
(A_IB)(C_{II}D)(B D_{III}P)

Wasike, J.-C.; Obrey, S. J.; Baker, T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001

Examples of Concurrent Tandem Catalysis

Examples where a Single Catalyst is Involved in Multiple Catalytic Systems

Parallel Recognition by Kinetic Control

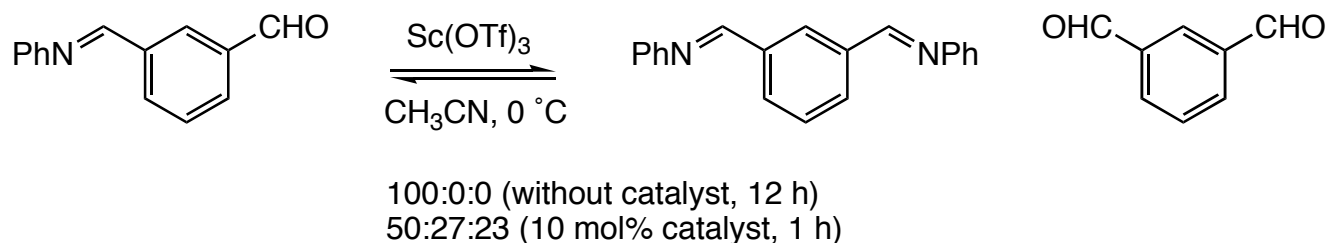


Conditions; Cat. 1 (10 mol%), diene (1.3 equiv), Sn(allyl)₄ (1.2 equiv), CH₃CN, 0 °C, 2 h

What makes this result interesting...

(AB₁C)(CD₁P)

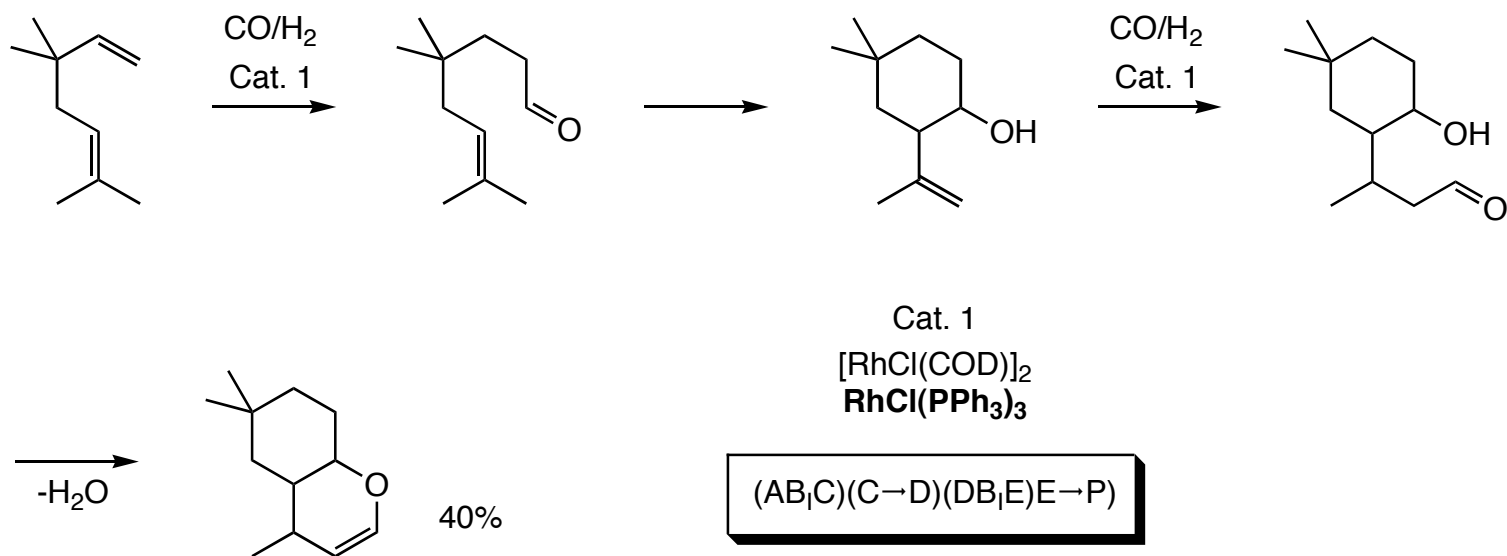
- The starting material is prone to redistribution



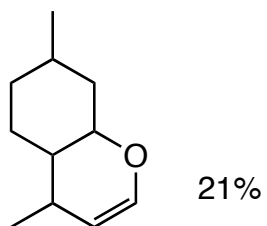
- Also, the **sequential addition** of both reagents gives lower yields (scrambling) and is less selective, especially for the allylation

Orita, A.; Nagano, Y.; Nakazawa, K.; Otera, J. *Adv. Synth. Catal.* **2002**, *344*, 548

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

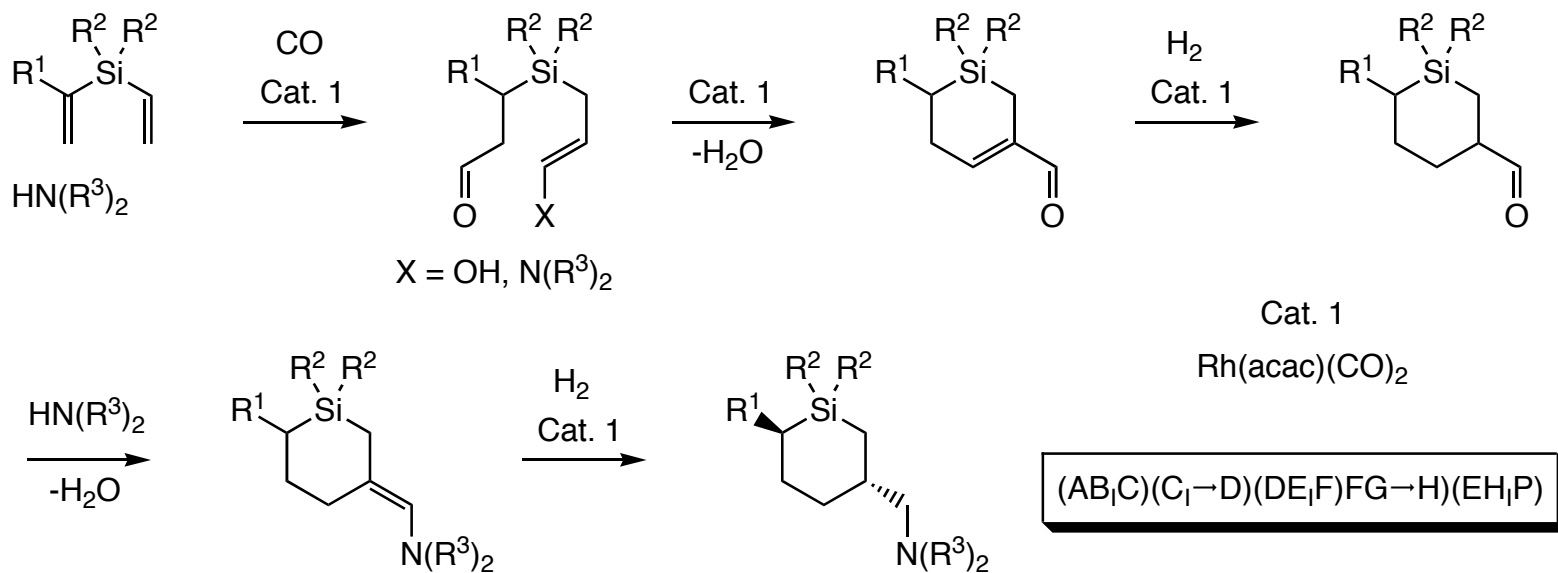


Conditions; Cat. 1 (1 mol%), PPh₃ (3 mol%), dioxane or toluene, CO (50 bar), H₂ (50 bar), 120 °C, 70 h

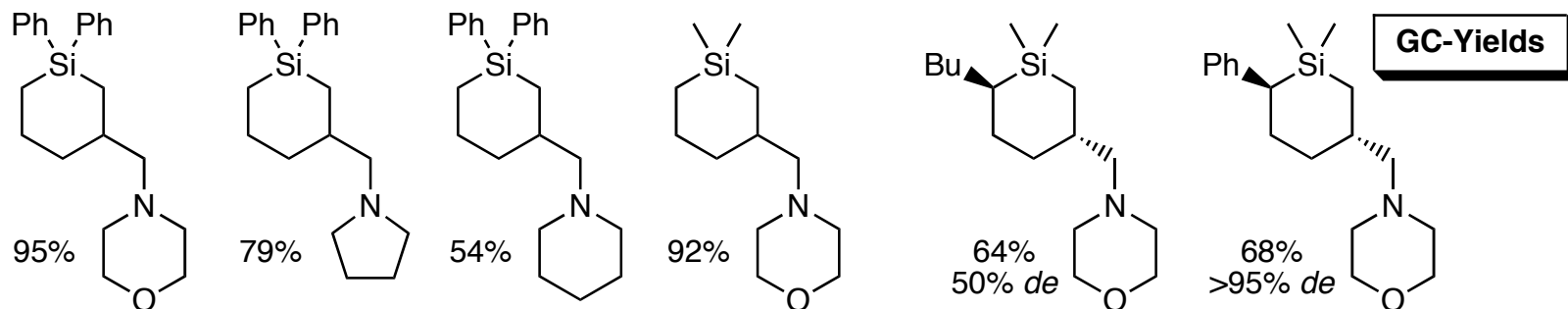


Roggenbuck, R.; Eilbracht, P. *Tetrahedron Lett.* **1999**, *40*, 7455

Silacyclohexanes by Hydroformylation/Aldol/Hydrogenation

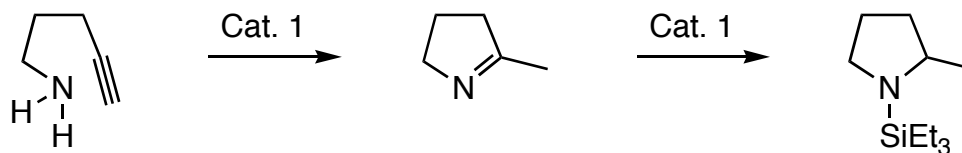


Conditions; Cat. 1 (1 mol%), PPh₃ (4 mol%), morpholine (2.7 equiv), CH₂Cl₂, CO (20 bar), H₂ (40 bar), 90 °C, 20-96 h

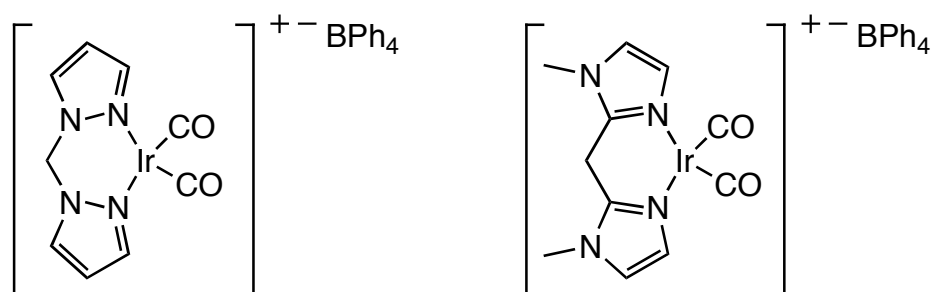


Bärfacker, L.; Tom, D. E.; Eilbracht, P. *Tetrahedron Lett.* **1999**, *40*, 4031

Concurrent Hydroamination/Hydrosilylation



Cat. 1

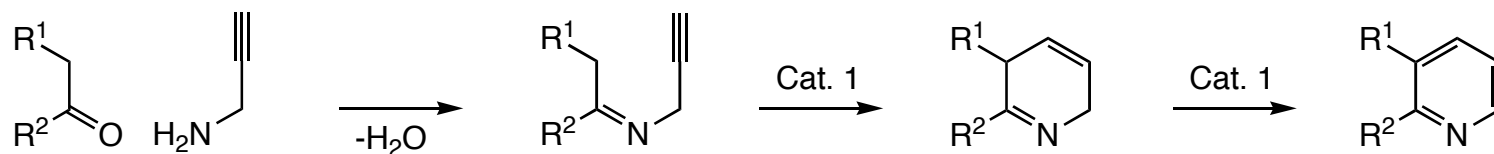


(A₁B)(BC₁P)

Conditions; Cat. 1 (2 mol%), Et₃SiH, THF-*d*₈, 60 °C (reaction monitored by ¹H NMR)

Field, L. D.; Messerle, B. A.; Wren, S. L. *Organometallics* **2003**, *22*, 4393

Amination/Annulation/Aromatization



Cat. 1

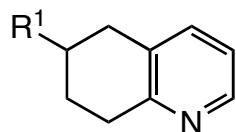
$\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$
 $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$

} 2 best catalysts

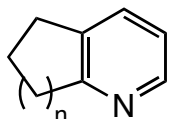
+ 19 other catalysts

(AB₁CD)(D₁P)

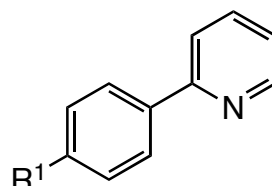
Conditions; Cat. 1 (2.5 mol%), EtOH, 78-100 °C, 5-24 h



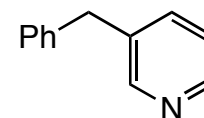
$R^1 = \text{Ph}$, 74%
 $R^1 = t\text{-Bu}$, 69%



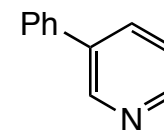
$n = 1$, 77%
 $n = 4$, 67%



$R^1 = \text{H}$, 78%
 $R^1 = \text{F}$, 66%
 $R^1 = \text{Br}$, 68%



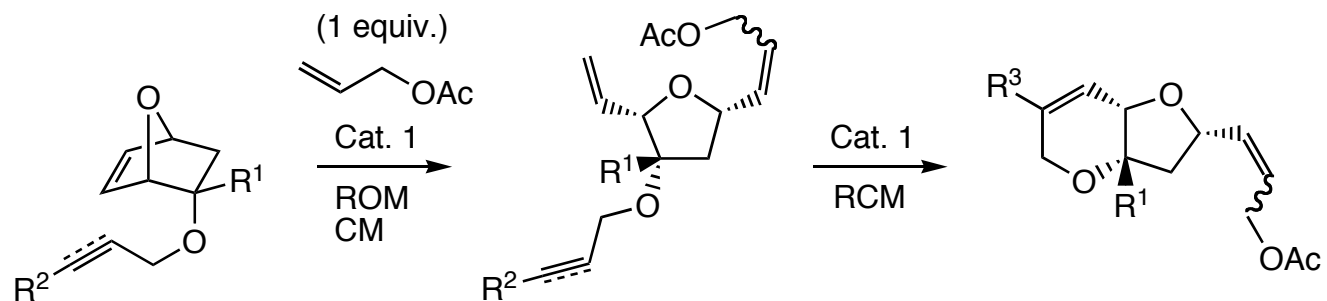
70%



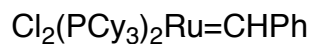
96%

Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959

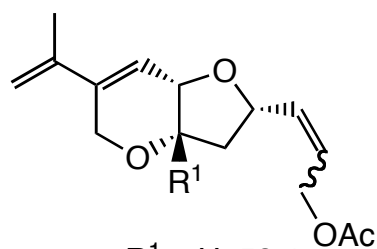
2,6-Dioxabicyclo[4.3.0]nonenes by ROM/CM/RCM



Cat. 1



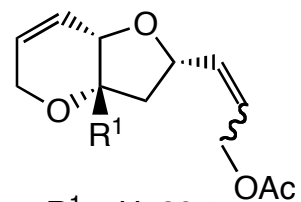
Conditions; Cat. 1 (8 mol%), CH_2Cl_2 , rt, 3 h



$\text{R}^1 = \text{H}$, 58%

$\text{R}^1 = \text{Ph}$, 60%

$\text{R}^1 = \text{Et}$, 55%



$\text{R}^1 = \text{H}$, 80%

$\text{R}^1 = \text{Ph}$, 90%

$\text{R}^1 = \text{Et}$, 70%

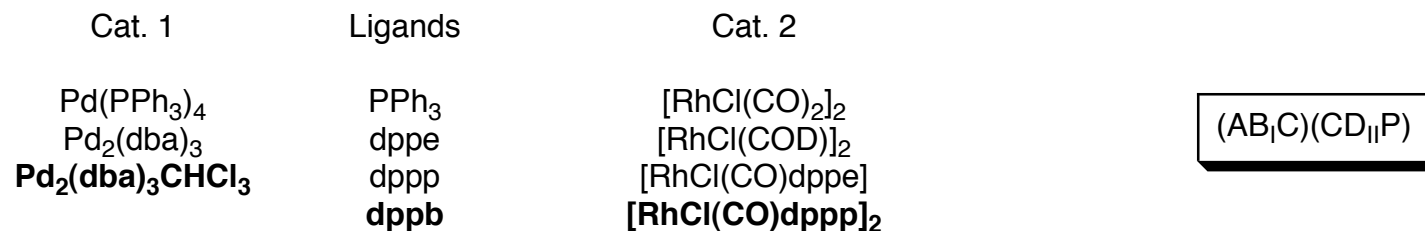
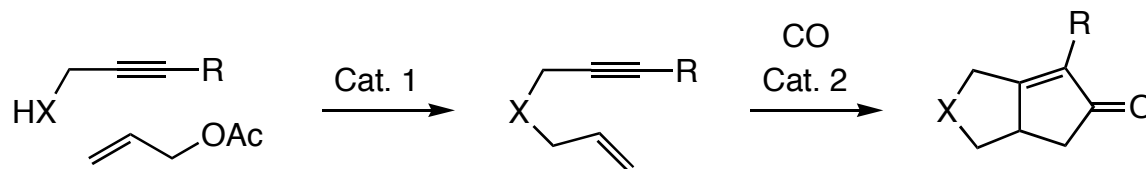
(AB₁C)(C₁D)(D₁P)

Arjona, O.; Csáky, A. G.; Murcia, M. C; Plumet, J. *Tetrahedron Lett.* **2000**, *40*, 9777

Examples of Concurrent Tandem Catalysis

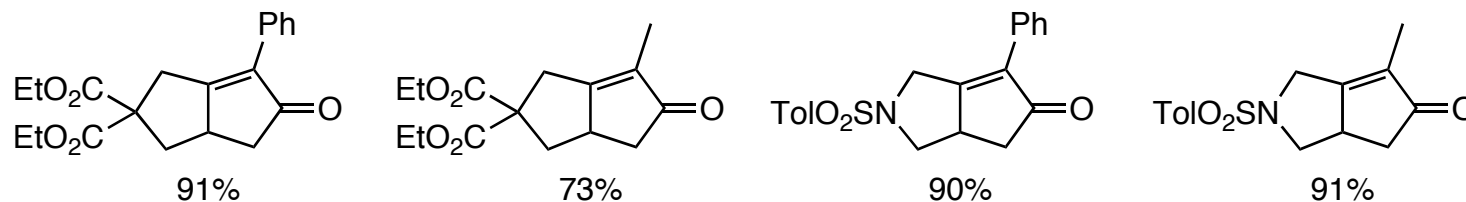
Examples where two Different Catalysts are Involved in Multiple Catalytic Systems

Bicyclopentenones by Allylation/Pauson-Khand Reaction



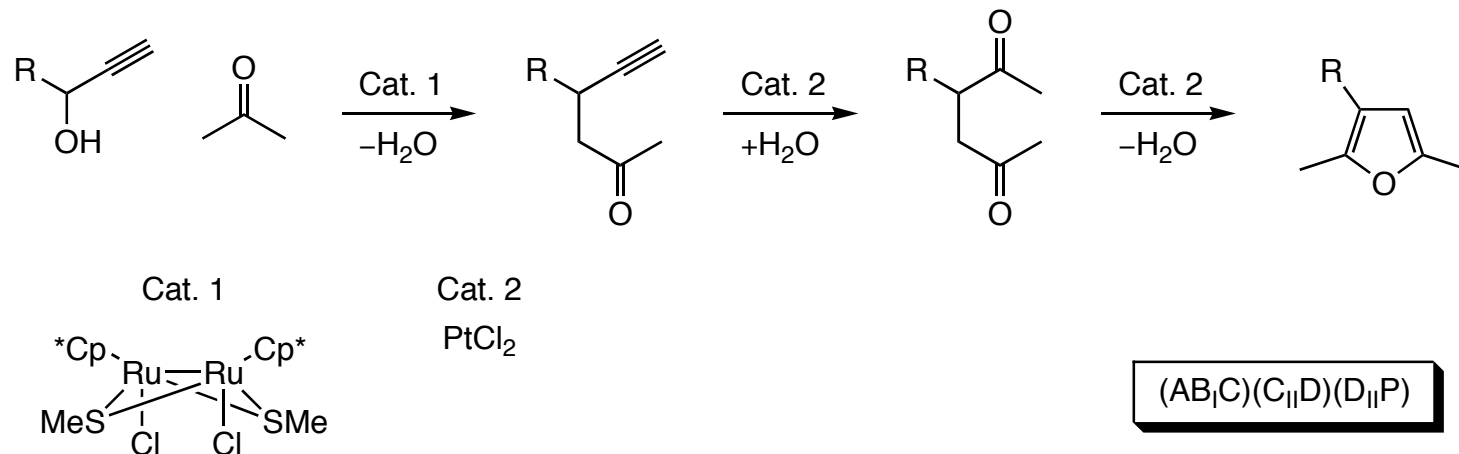
Conditions; Cat.1 (1.5 mol%), dppb (3.0 mol%), BSA (1.2 equiv), Cat. 2 (7 mol%), Toluene, CO (1 atm), 110 °C, 35 h

BSA = bis(trimethylsilyl)acetamide

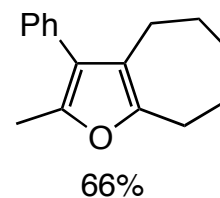
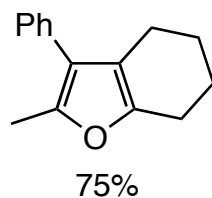
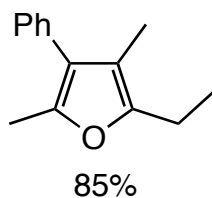
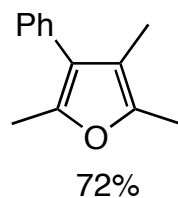


Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220

Furanes by Propargylic Substitution/Hydration/Cyclization

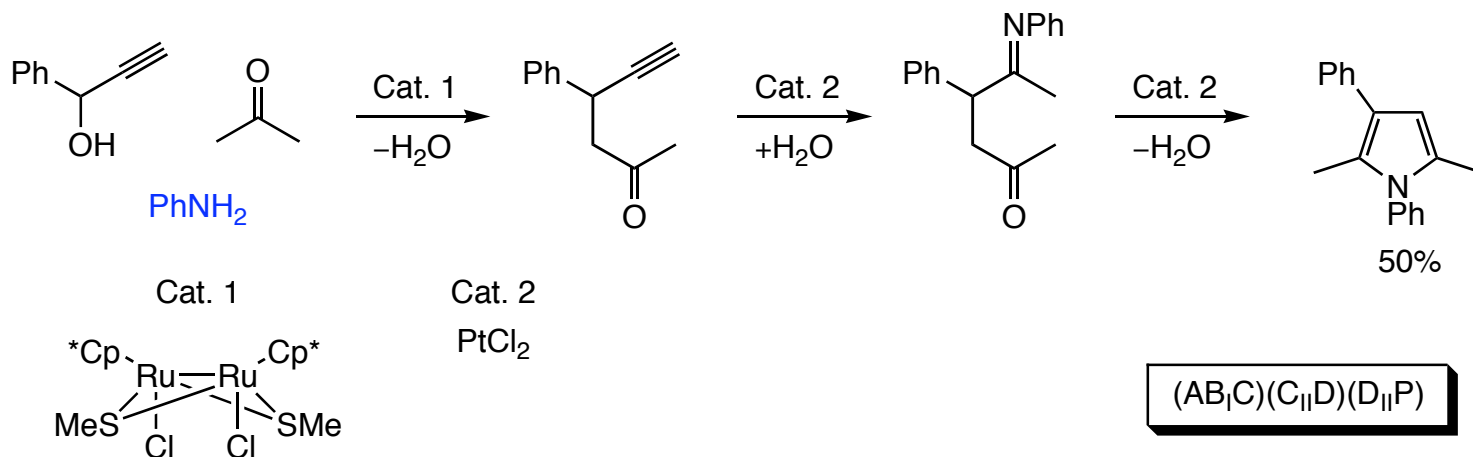


Conditions; Cat. 1 (10 mol%), NH₄BF₄ (20 mol%), Cat. 2 (20 mol%), acetone, reflux, 36–72 h

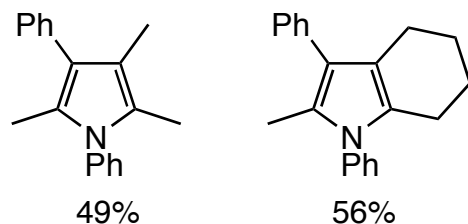


Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 2681

Furanes by Propargylic Substitution/Hydration/Cyclization

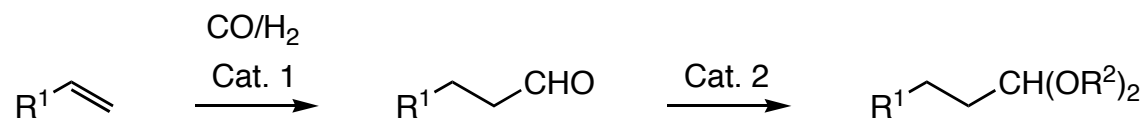


Conditions; Cat. 1 (10 mol%), NH₄BF₄ (20 mol%), Cat. 2 (20 mol%), acetone, reflux, 100 h



Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 2681

Acetals by Hydroformylation/Acetalization of Alkenes

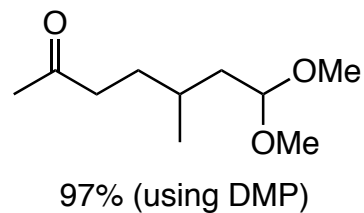
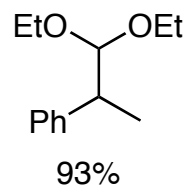
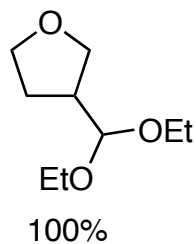


Cat. 1
[Rh₂(μ-OMe)₂(COD)₂]

Cat. 2
PPTS
SnCl₂ and PTSA not successful

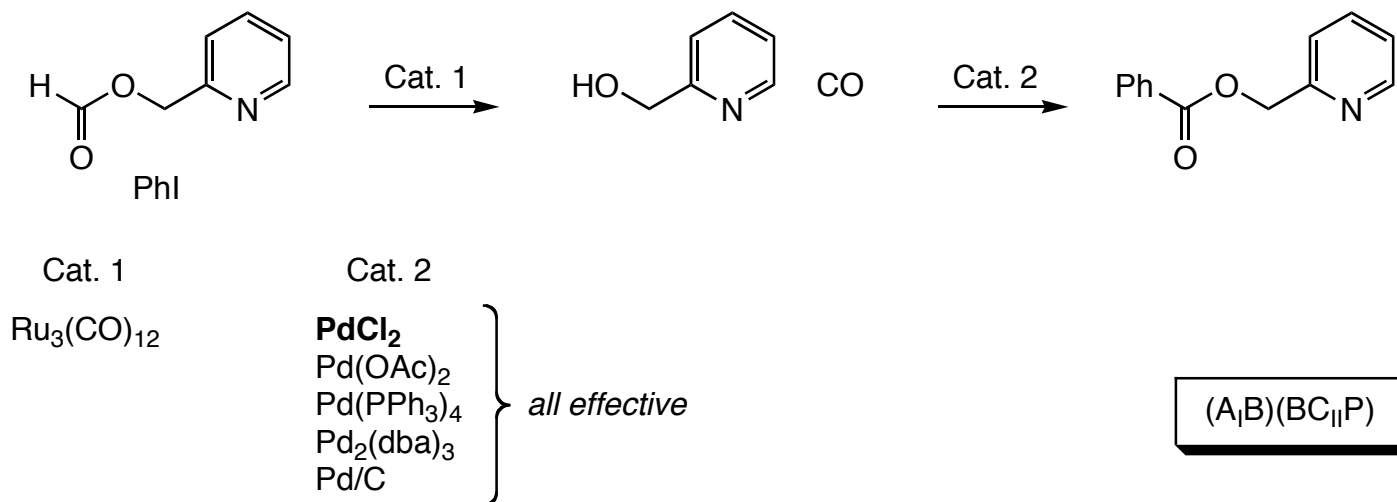
(A₁B)(B₁₁P)

Conditions; Cat. 1 (1 mol%), PPh₃ (10 mol%), Cat. 2 (5 mol%), HC(OEt)₃, 60 °C, CO/H₂, 50 bar 12-24 h

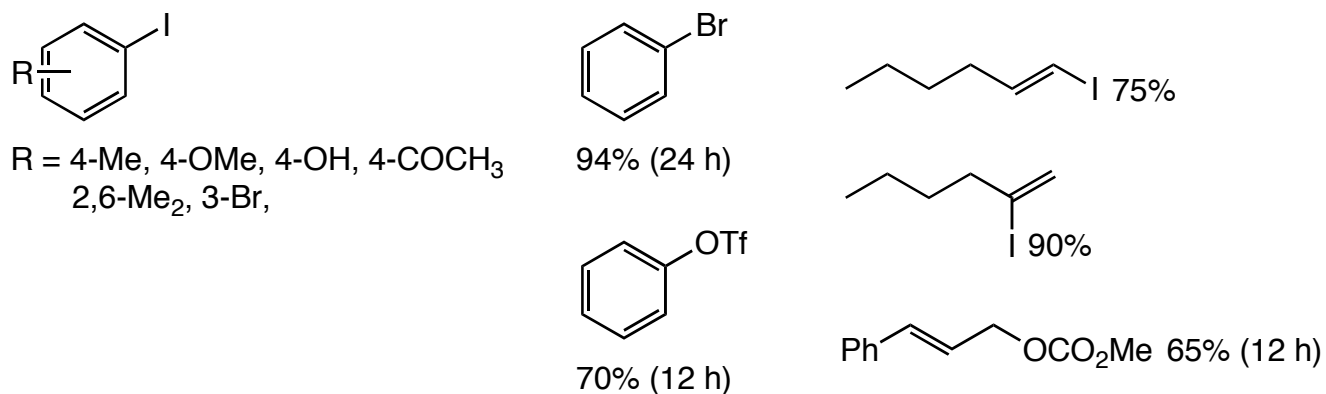


Fernández, E.; Castellón, S. *Tetrahedron Lett.* **1994**, *35*, 2361

Formate Decarbonylation/Aryl Halide Alkoxyacylation

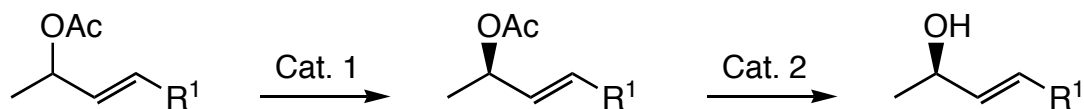


Conditions; Cat. 1 (3 mol%), Cat.2 (2 mol%), NaHCO₃, DMF, 135 °C



Ko, S.; Lee, C.; Choi, M.-G.; Na, Y.; Chang, S. *J. Org. Chem.* **2003**, *68*, 1607

DKR of Allylic Acetates/Transesterification



Cat. 1

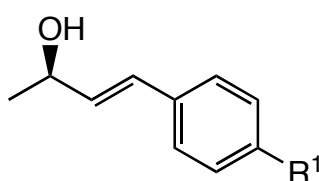
Cat. 2

$\text{Pd}(\text{PPh}_3)_4$

***Candida antarctica* lipase B
(CALB, Novozym 435)
Pseudomonas cepacia lipase**

(A₁B)(B₁A)(A₁₁P)

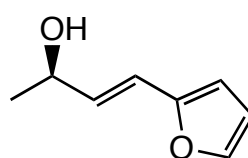
Conditions; Cat. 1 (5 mol%), dppf (15 mol%), *i*-PrOH (10 equiv), Cat. 2 (200-400 mg/mmol), THF, rt, 1.5-3 d



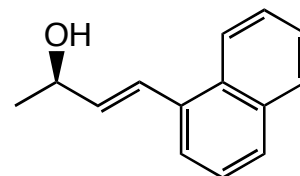
R¹ = H, 71%(98)

R¹ = Cl, 67%(97)

R¹ = Me, 70%(98)



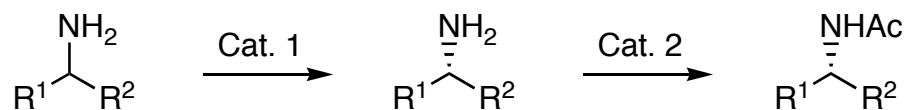
78%(99)



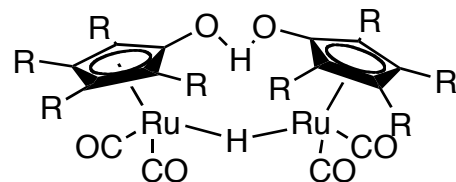
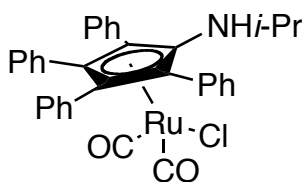
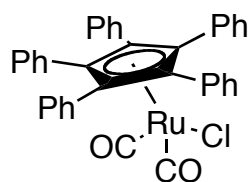
61%(98)

Choi, Y. K.; Suh, J. H.; Lee, D.; Lim, I. T.; Jung, J. Y.; Kim, M.-J. *J. Org. Chem.* **1999**, *64*, 8423

Chemoenzymatic DKR/Acylation



Cat. 1



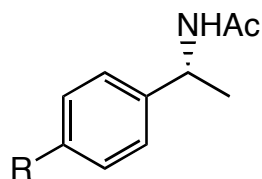
R = Ph, *p*-F-C₆H₄, *p*-OMe-C₆H₄

Cat. 2

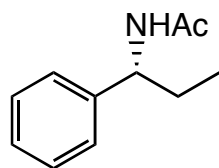
Candida antarctica lipase B
(CALB, Novozym 435)

(A₁B)(B₁A)(A₁₁P)

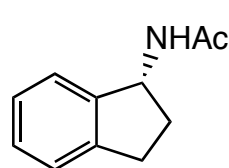
Conditions; Cat. 1 (4 mol%), *i*-PrOAc, Cat. 2 (40 mg/mmol of amine), Na₂CO₃, Toluene, 90 °C, 3 d



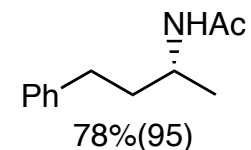
R = H, 90%(98)
R = F, 83%(99)
R = Br, 78%(99)
R = OMe, 95%(99)
R = CF₃, 91%(99)



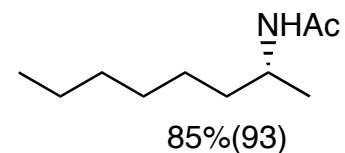
85%(99)



92%(95)



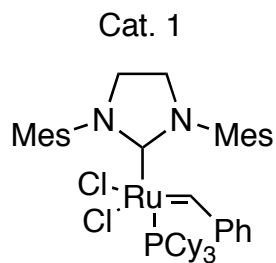
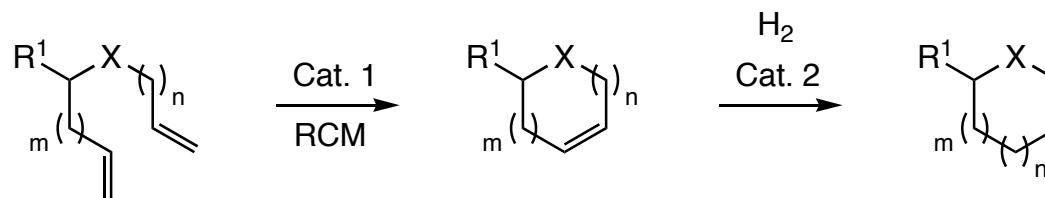
78%(95)



85%(93)

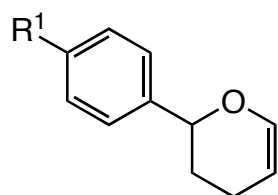
Paetzold, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620

Cyclic Enol Ethers by RCM/Olefin Isomerization

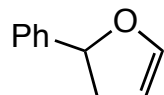


(A₁B)(I→II)(B_{II}P)

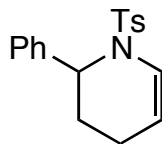
Conditions; Cat. 1 (10 mol%), CH₂Cl₂, N₂/H₂ (95:5, 1 atm), 45-70 °C, 6-12 h



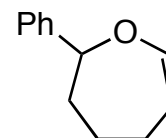
R¹ = H, 61%
R¹ = OMe, 65%
R¹ = Cl, 58%



46%



74%

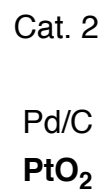
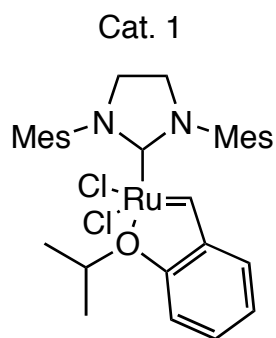
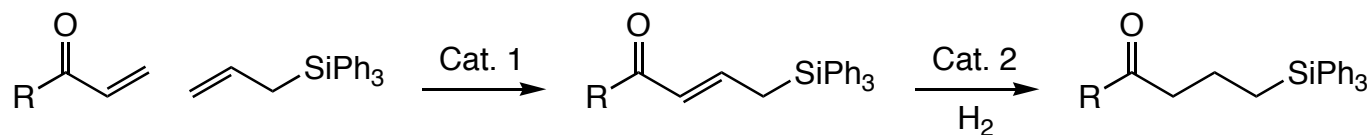


54%

<10% olefin hydrogenation obtained

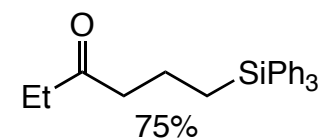
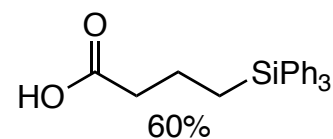
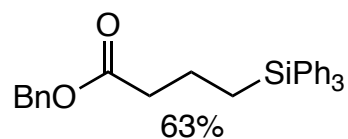
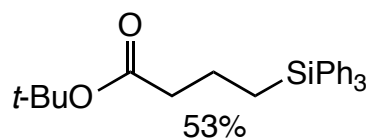
Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390

Cross-Metathesis/Hydrogenation



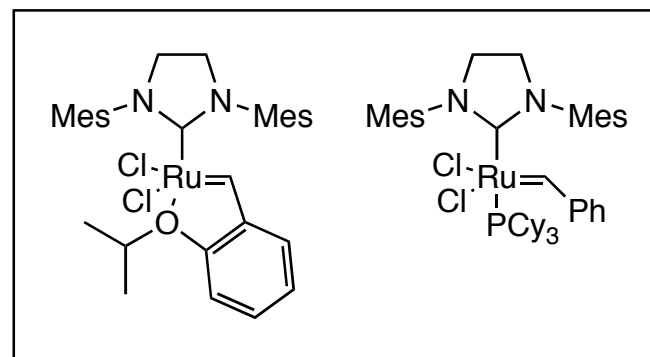
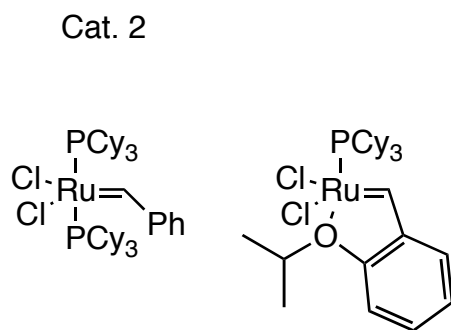
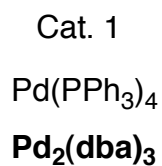
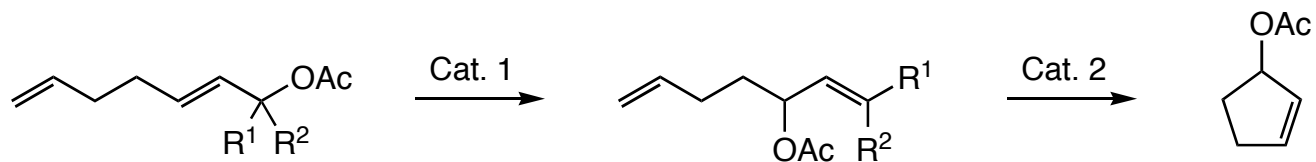
(AB₁C)(C₁₁P)

Conditions; Cat. 1 (5 mol%), Cat. 2 (5 mol%), CH₂Cl₂, H₂ (1 atm), rt, 15 h



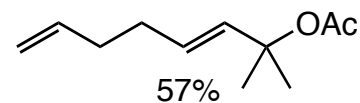
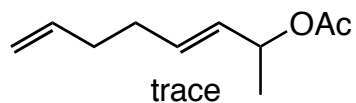
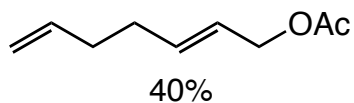
Cossy, J. Bargiggia, F. C.; Bouzbouz, S. *Tetrahedron Lett.* **2002**, *43*, 6715

Allylic Acetate Isomerization/Ring-Closing Metathesis



Conditions; Cat. 1 (5 mol%), PPh_3 (20 mol%), Cat.2 (5 mol%), CDCl_3 , rt, 20 h

(A₁B)(B₁₁P)



Braddock, D. C.; Wildsmith, A. J. *Tetrahedron Lett.* **2001**, 42, 3239
 Braddock, D. C.; Matsuno, A. *Tetrahedron Lett.* **2002**, 43, 3305

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."*

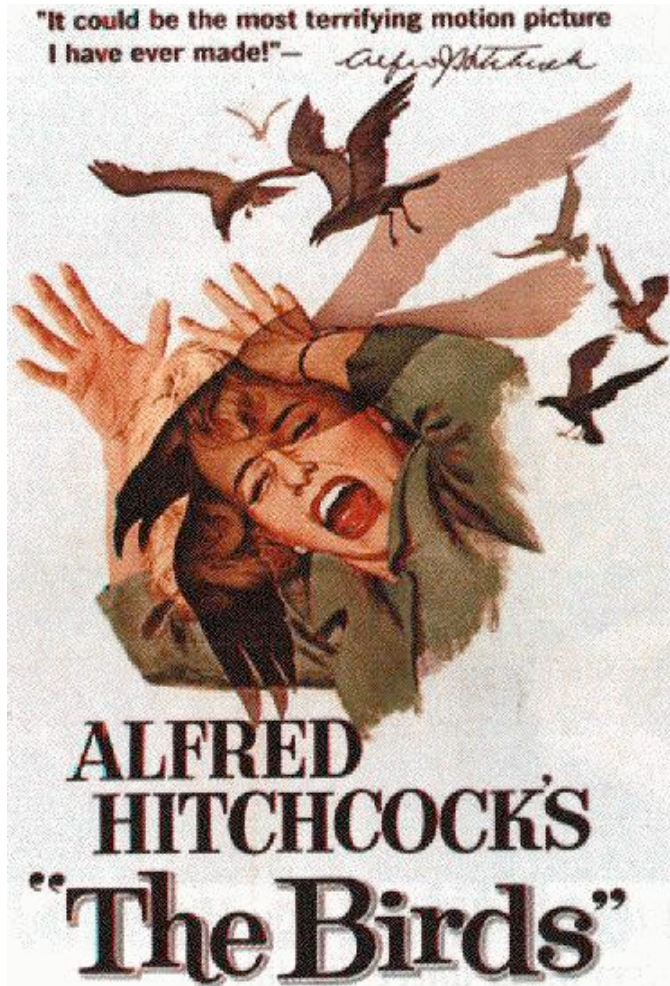
 - *"...matching the rates of the individual catalytic cycles."*
Insight into mechanism, ability to control TOF, transferring cycle products within the same medium

 - *"Characterization of active sites in heterogeneous catalysts..."*

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

Wasike, J.-C.; Obrey, S. J.; Baker, T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001

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, rhinorrhoea 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 exacerbations of pre-existing disease such as asthma and chronic obstructive pulmonary disease (COPD)."*
- *"Much rarer systemic complications include myositis, myocarditis and encephalitis."*

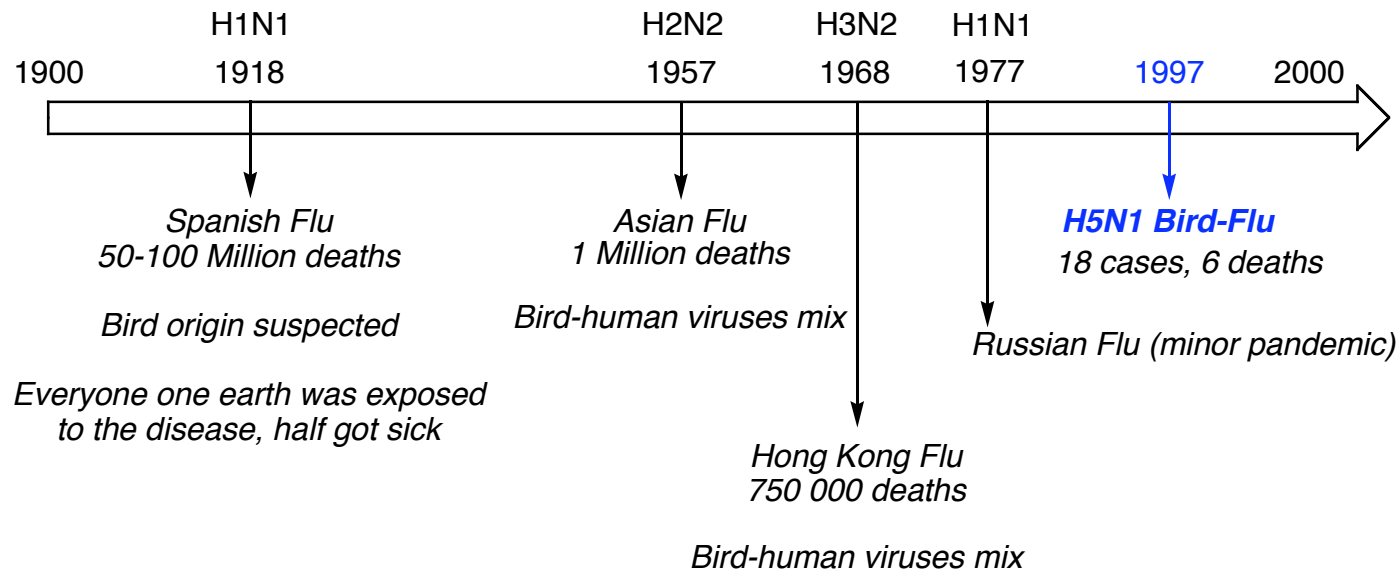
Johnston, L. S. *Virus Res.* **2002**, 82, 147

Influenza (Flu): The Pandemics of the 20th Century

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

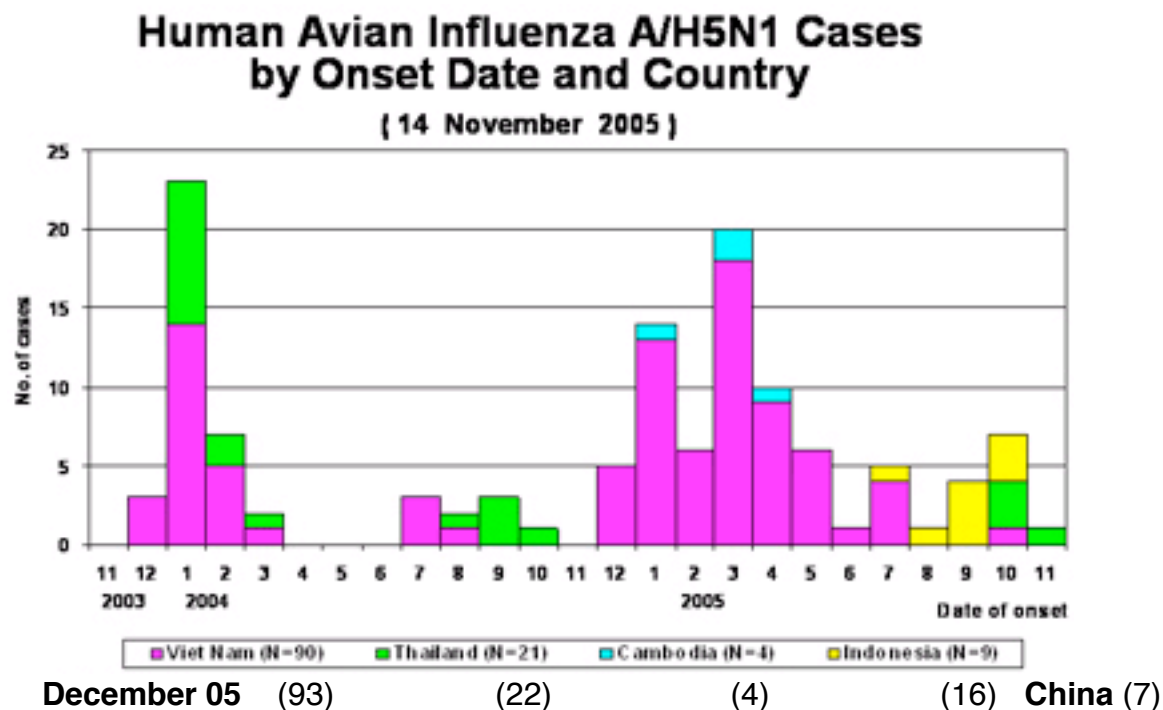
- According to the World Health Organisation (WHO) 3 to 5 million cases of seasonal influenza occur every year (250 000-500 000 die, mostly the elderly, the very young and those who have underlying respiratory and cardiovascular disease).

• Timeline of the pandemics of the 20th Century



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..."



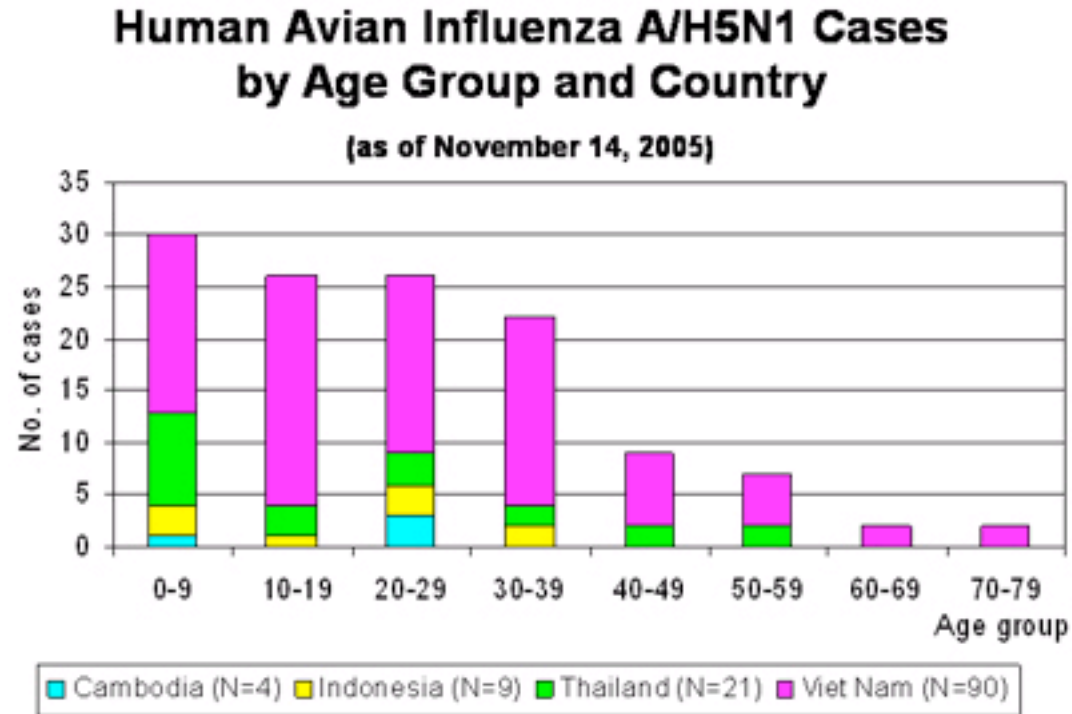
http://www.checkflu.com/tracking_influenza.html

- First reported case outside of Asia happened in Turkey.

New Engl. J. Med. 2005, 353, 1374

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."

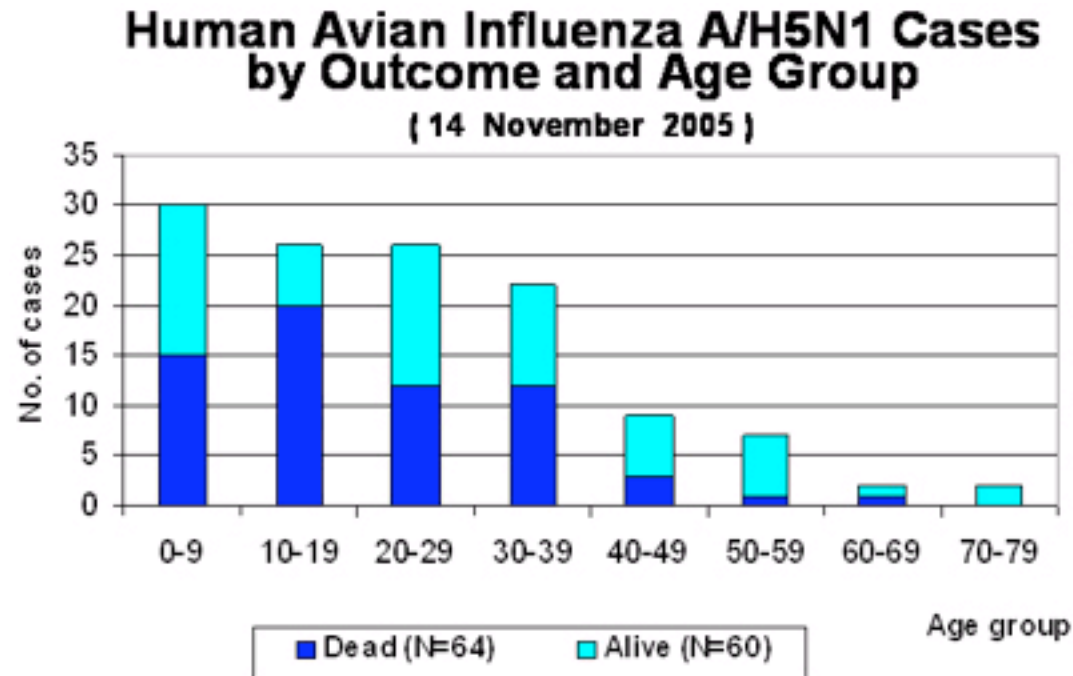


http://www.checkflu.com/tracking_influenza.html

New Engl. J. Med. 2005, 353, 1374

Global Incidence of the Human Influenza A (H5N1)

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http://www.checkflu.com/tracking_influenza.html

New Engl. J. Med. 2005, 353, 1374

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?

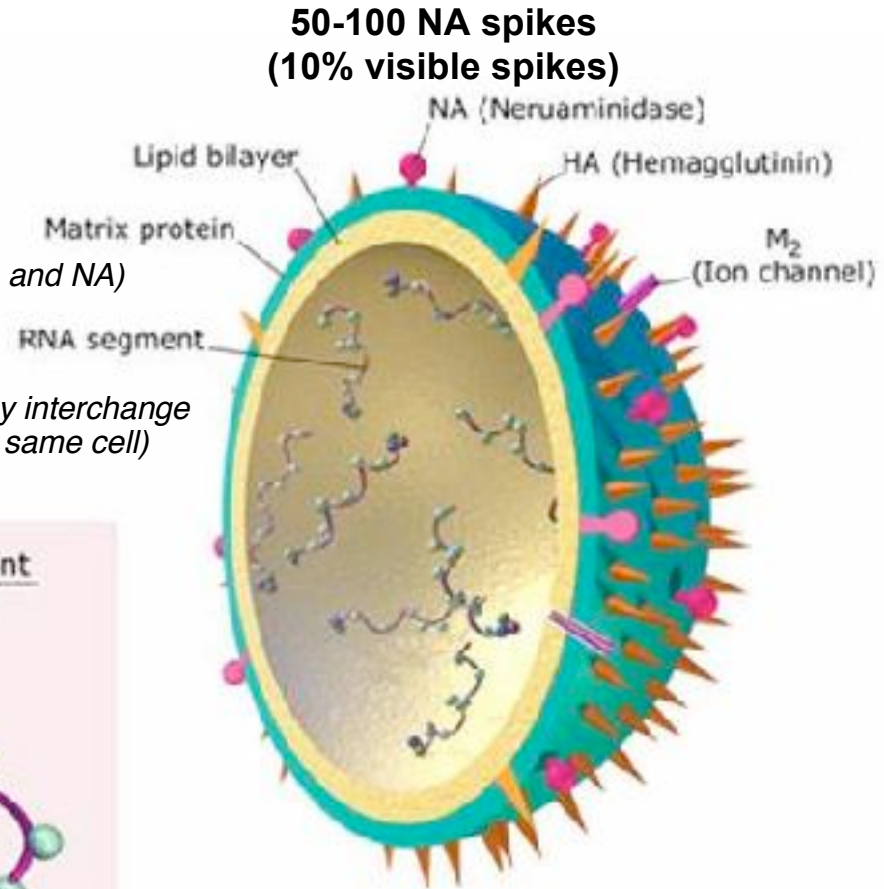
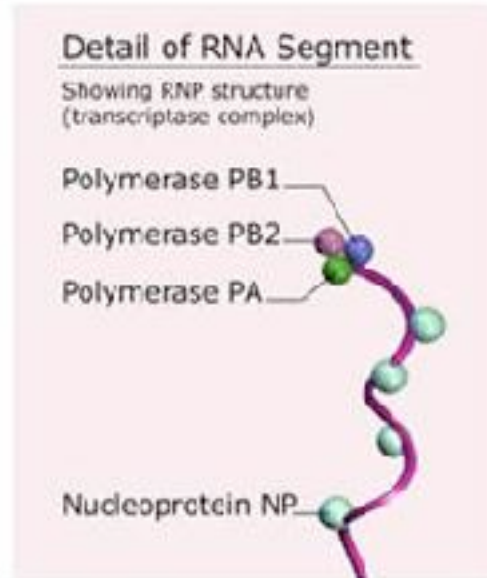
Glycoproteins

- 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



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."*

Antigenic Drift

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

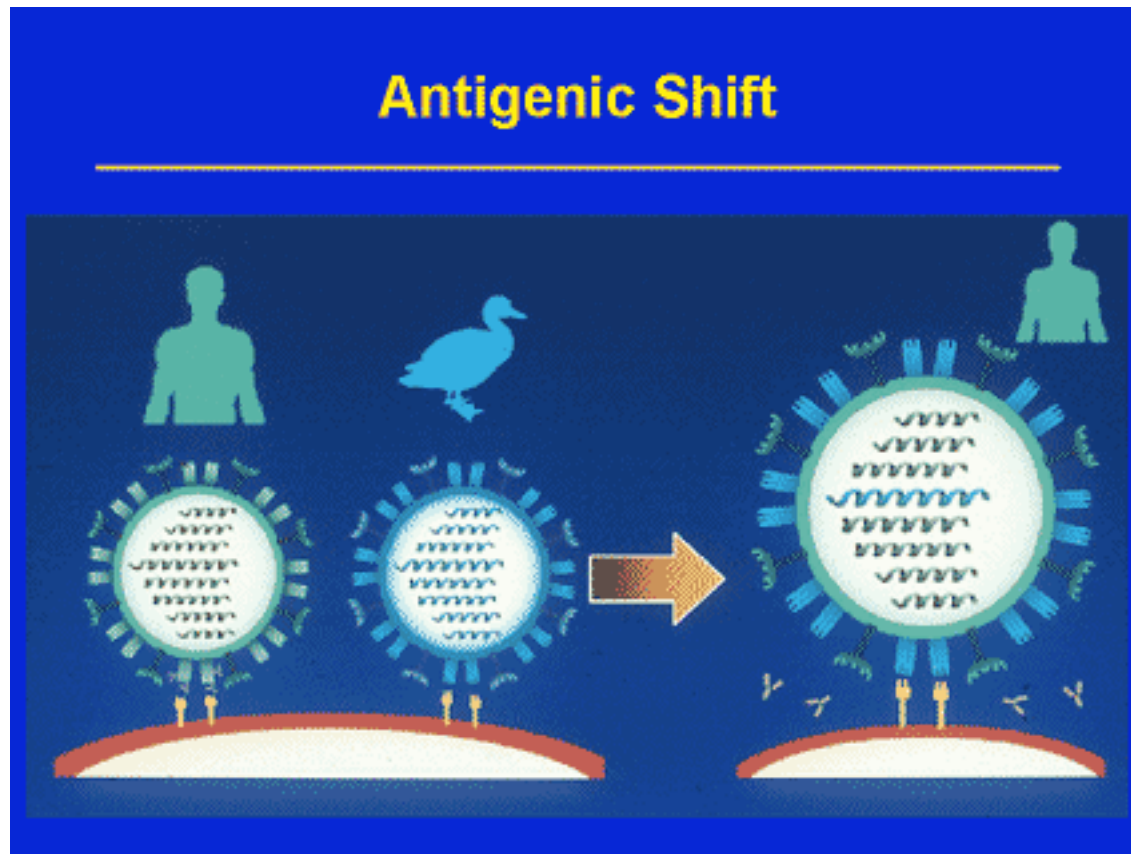
*A bird strain of Influenza A can directly jump to humans
A virus can jump to an intermediate host (such as a pig) and then to humans
Genetic mixing, after two flu strains meet in the same cell*

Antigenic Shift

- *"...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."*

Varghese, J. N. *Drug Dev. Res.* **1999**, 46, 176

Why/How do Pandemics occur?



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

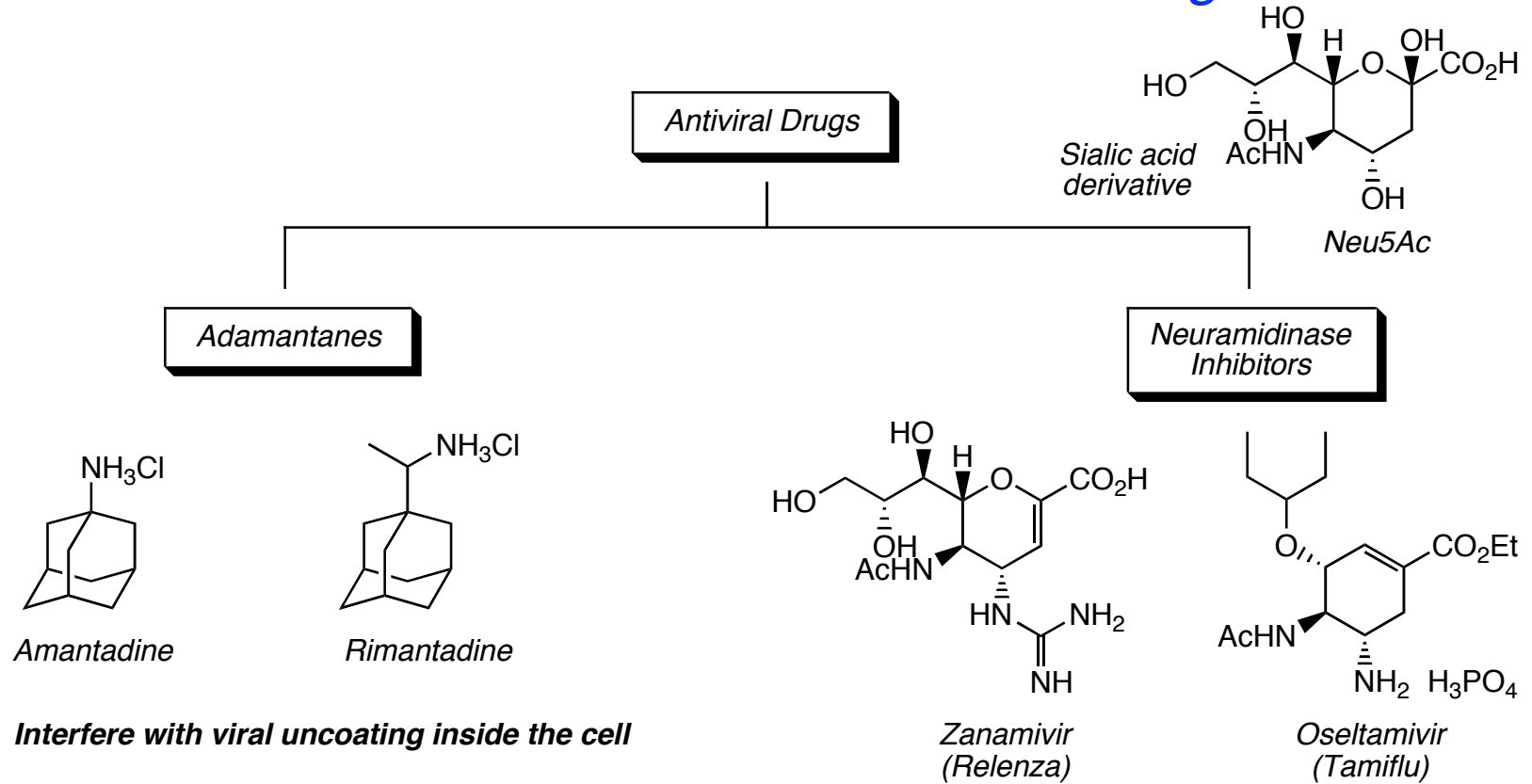
Rare strain
Only present in humans

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

Varghese, J. N. *Drug Dev. Res.* **1999**, 46, 176

What are the available antiviral drugs?

What are the Available Antiviral Drugs?



Interfere with viral uncoating inside the cell

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*

Moscona, A. *New Engl. J. Med.* **2005**, 353, 1363

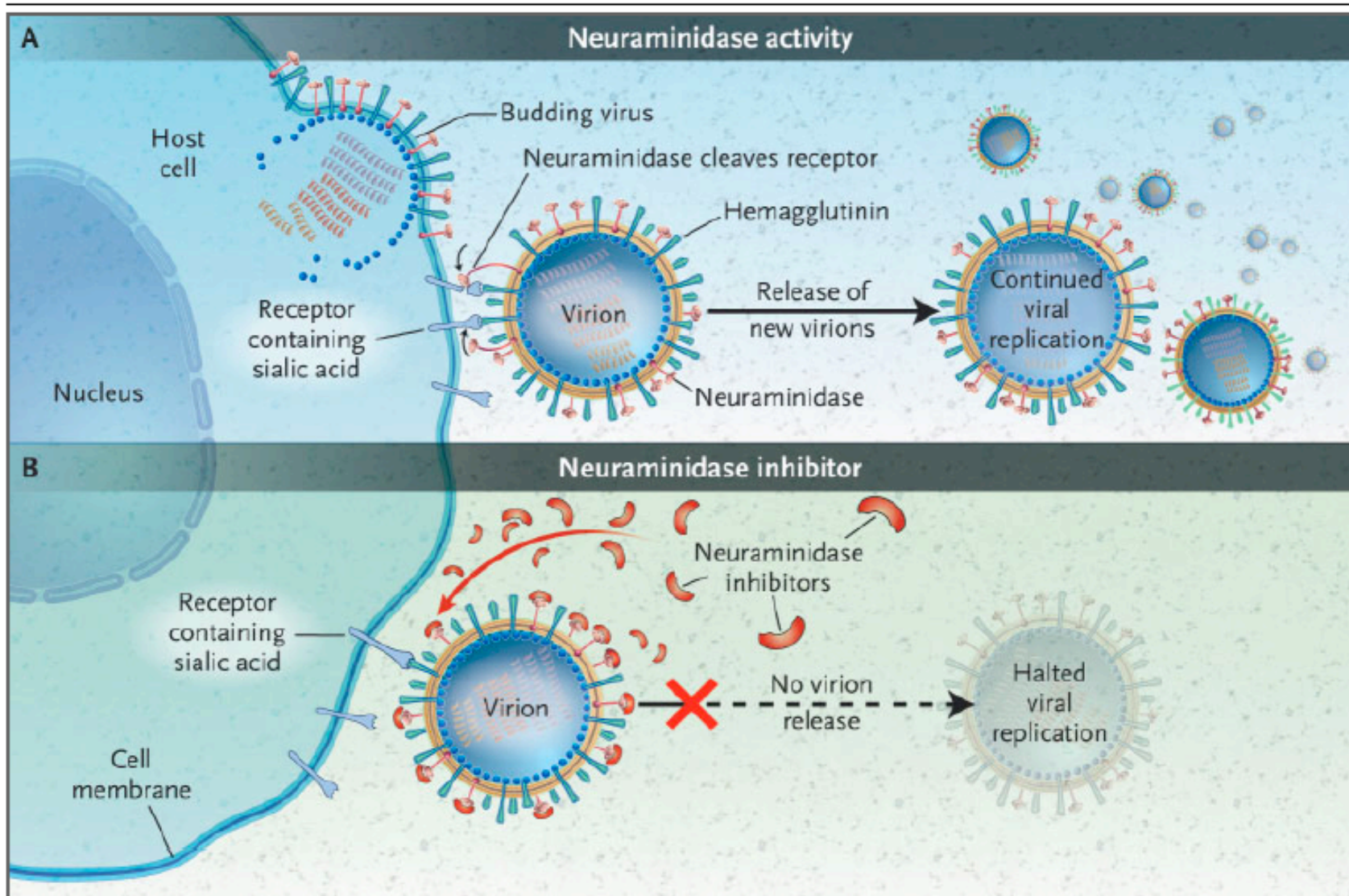


Figure 1. Mechanism of Action of Neuraminidase Inhibitors.

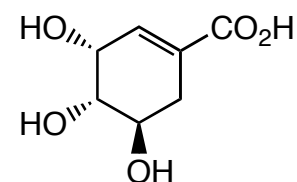
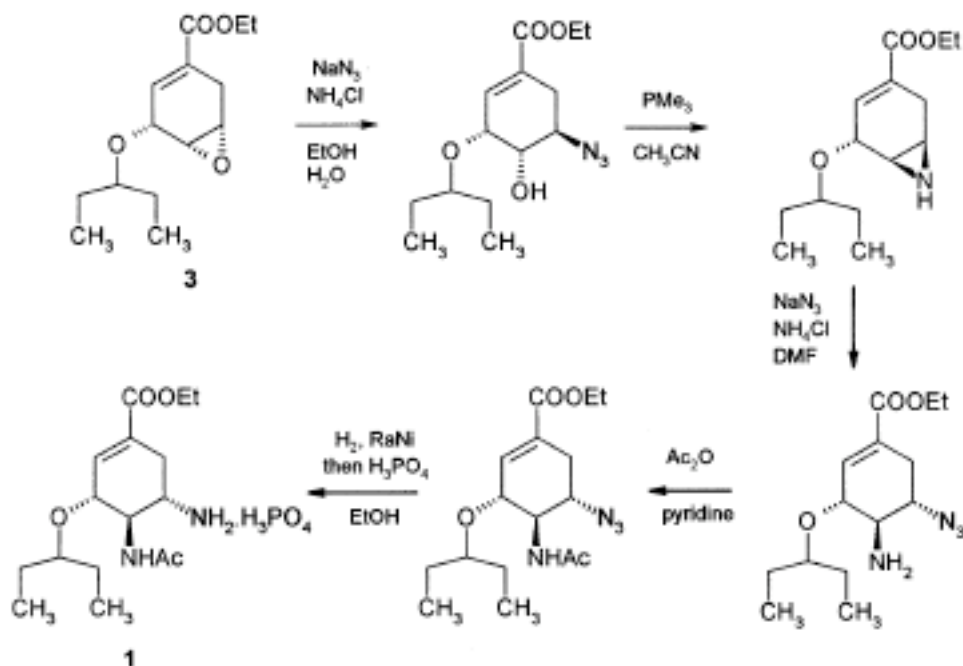
Panel A shows the action of neuraminidase in the continued replication of virions in influenza infection. The replication is blocked by neuraminidase inhibitors (Panel B), which prevent virions from being released from the surface of infected cells.

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

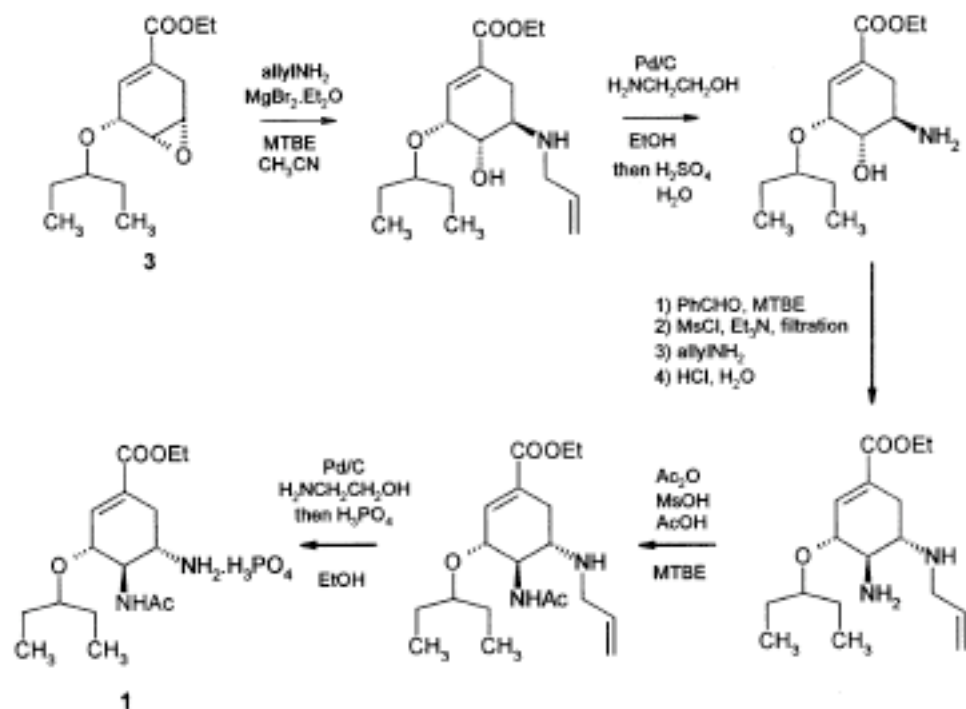
Scheme 1. Gilfed route to oseltamivir phosphate 1



Rohloff, J. C *et al.* *J. Org. Chem.* **1998**, *63*, 4545

Tamiflu: Second Approach

Scheme 2. Roche-Basel route to oseltamivir phosphate 1

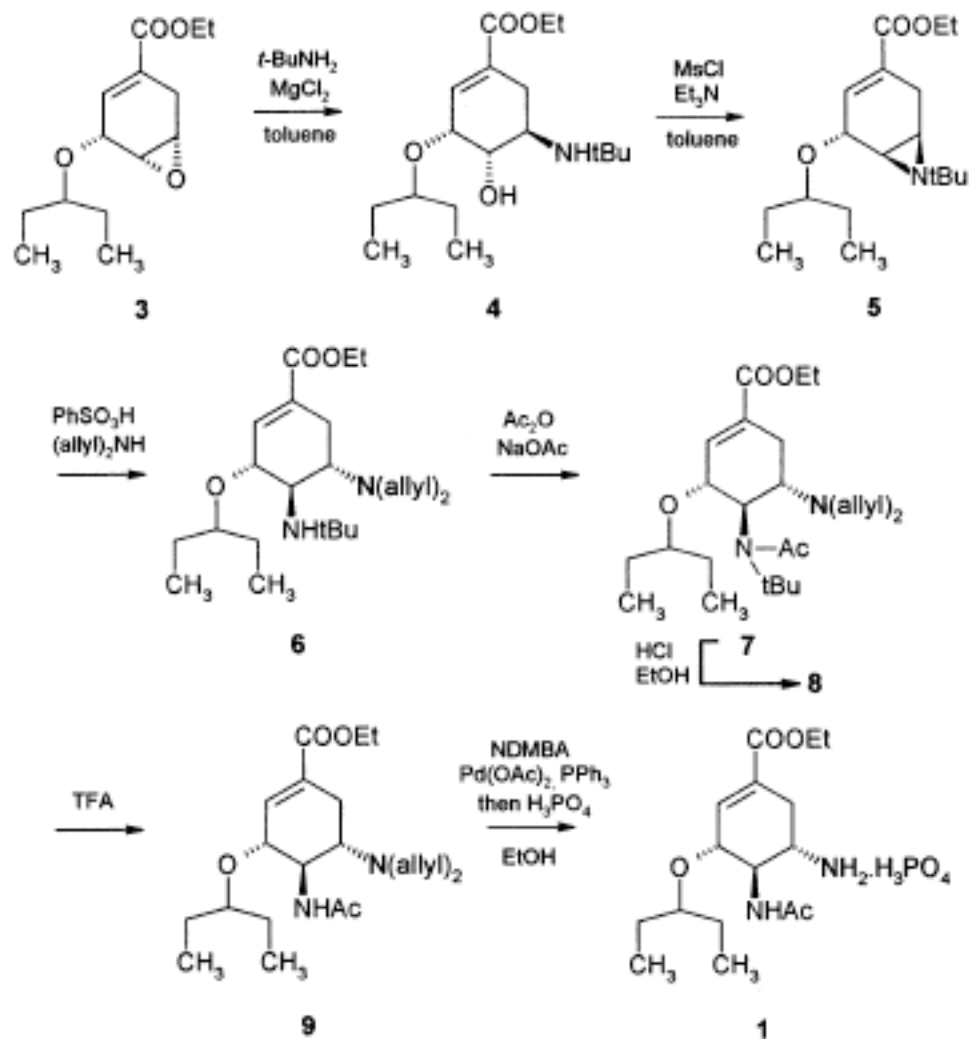


Azide-free approach

Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044

Tamiflu: Third Approach

Scheme 3. Second-generation route to oseltamivir phosphate **1**



Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Proc. Res. Dev.* **2004**, *8*, 86

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."*