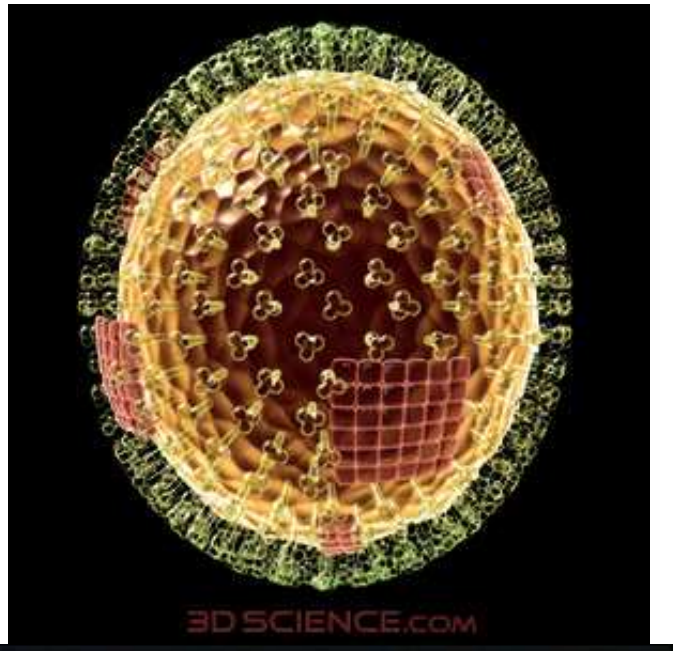
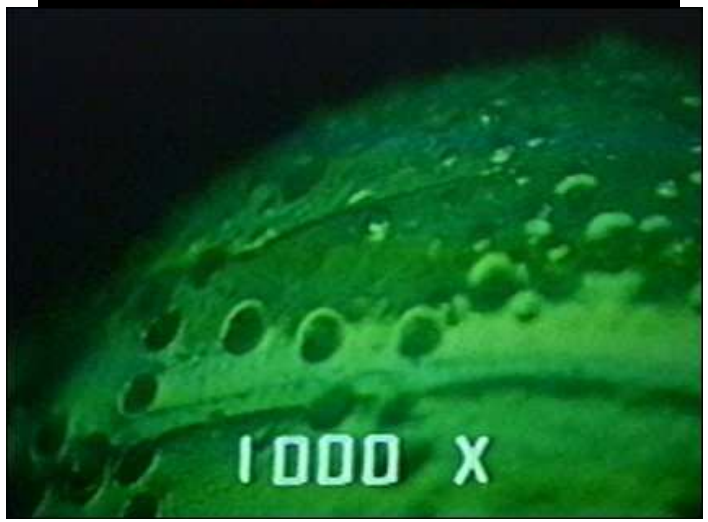
# Syntheses of Oseltamivir– the cure for the flu?


Philip Williams
Crimmins Group
January 14, 2009

# The Flu – Background Facts

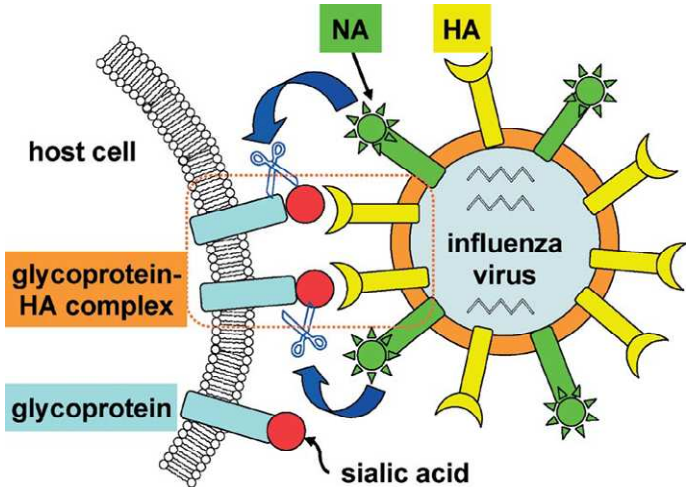
- Influenza is an RNA virus that is highly capable of mutating – making it extremely hard to prevent.
- In the U.S., an estimated 25–50 million cases/yr
- 150,000 hospitalizations and 30,000–40,000 deaths
- Extrapolated to the global population, this equates to 1 billion cases of flu, around 3–5 million cases of severe illness, and 300,000–500,000 deaths annually.
- Early antivirals inhibited the M2 proton channel, which was effective only against one strain (influenza A), and the drugs had a number of side effects and have also become resistant.
- Avian Flu Strain: H5N1
  - Avain strains have been source of major influenza epidemics in history.
- Influenza A – birds, aquatic animals, rarely humans
- Influenza B – Humans, seals
- Influenza C – humans and pigs – very rare

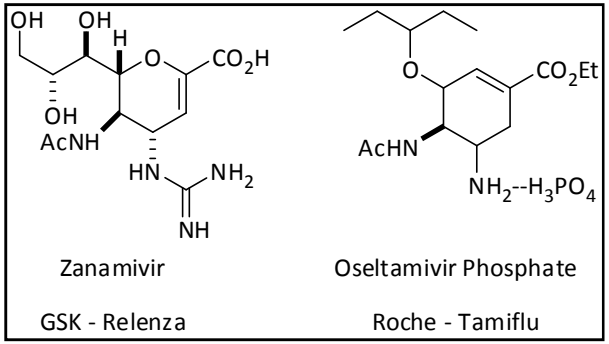


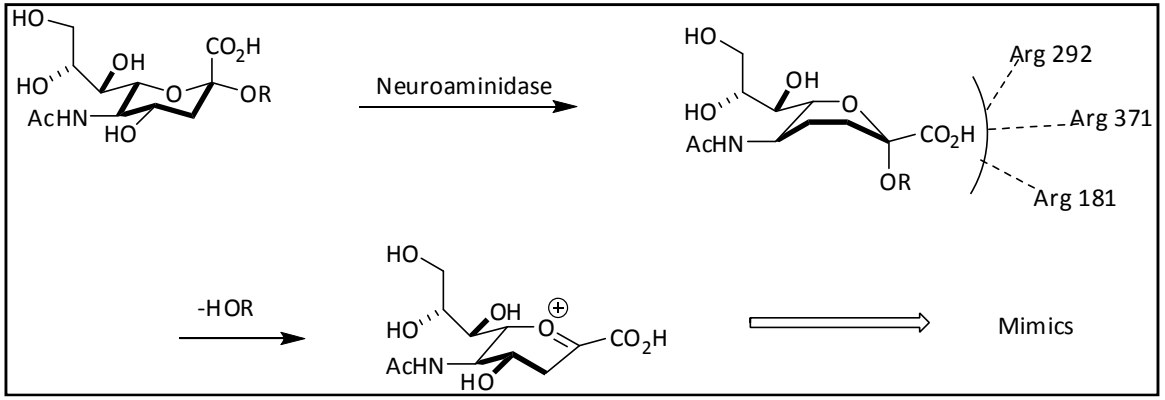



# The Flu – A Common Approach

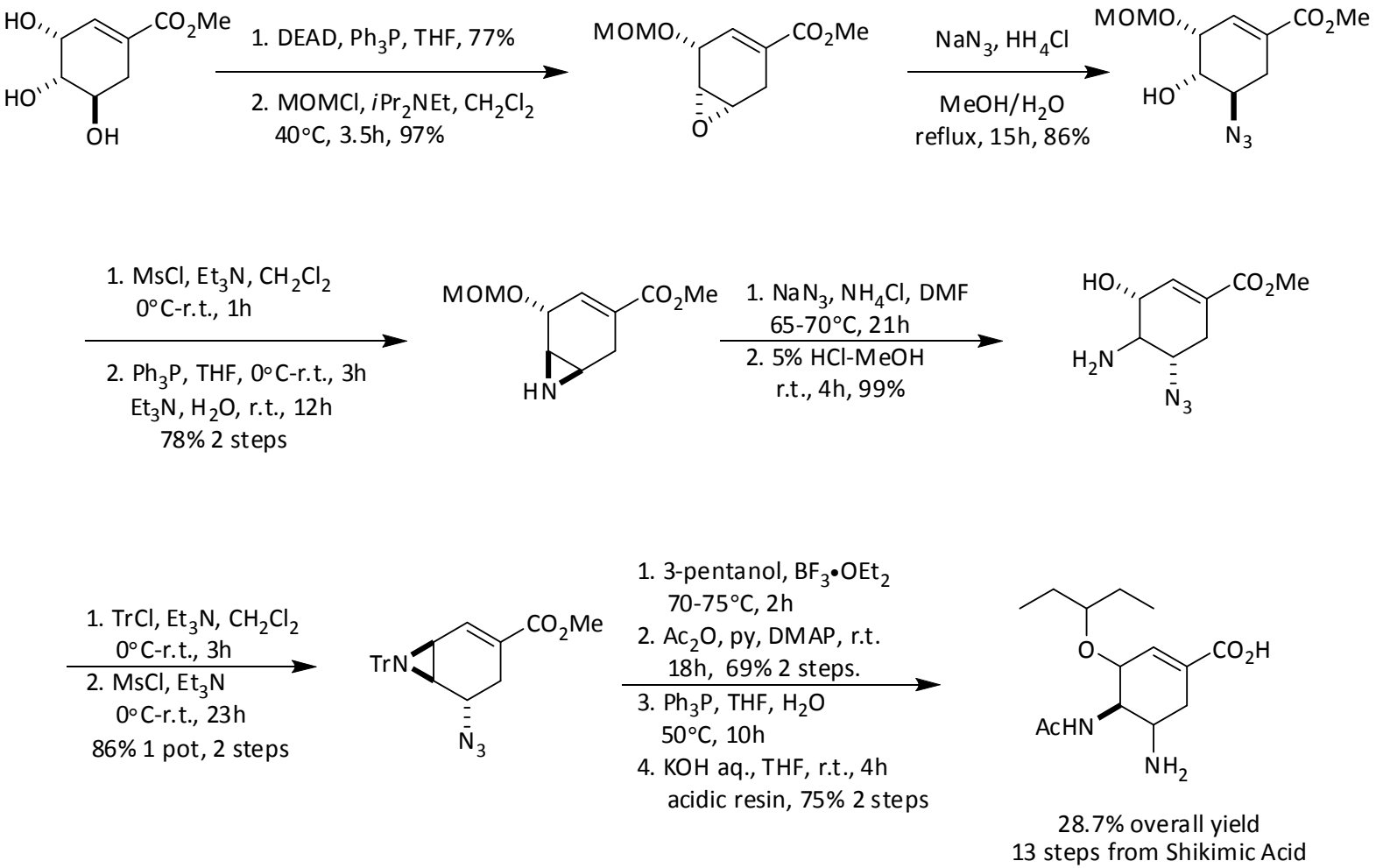
- M2 proton channel not conserved throughout influenza strains
- Prediction – most essential processes will be conserved.
- Neuroaminidase conserved in both Influenza A and B.
- Tamiflu – $IC_{50}$ is in nanomolar range



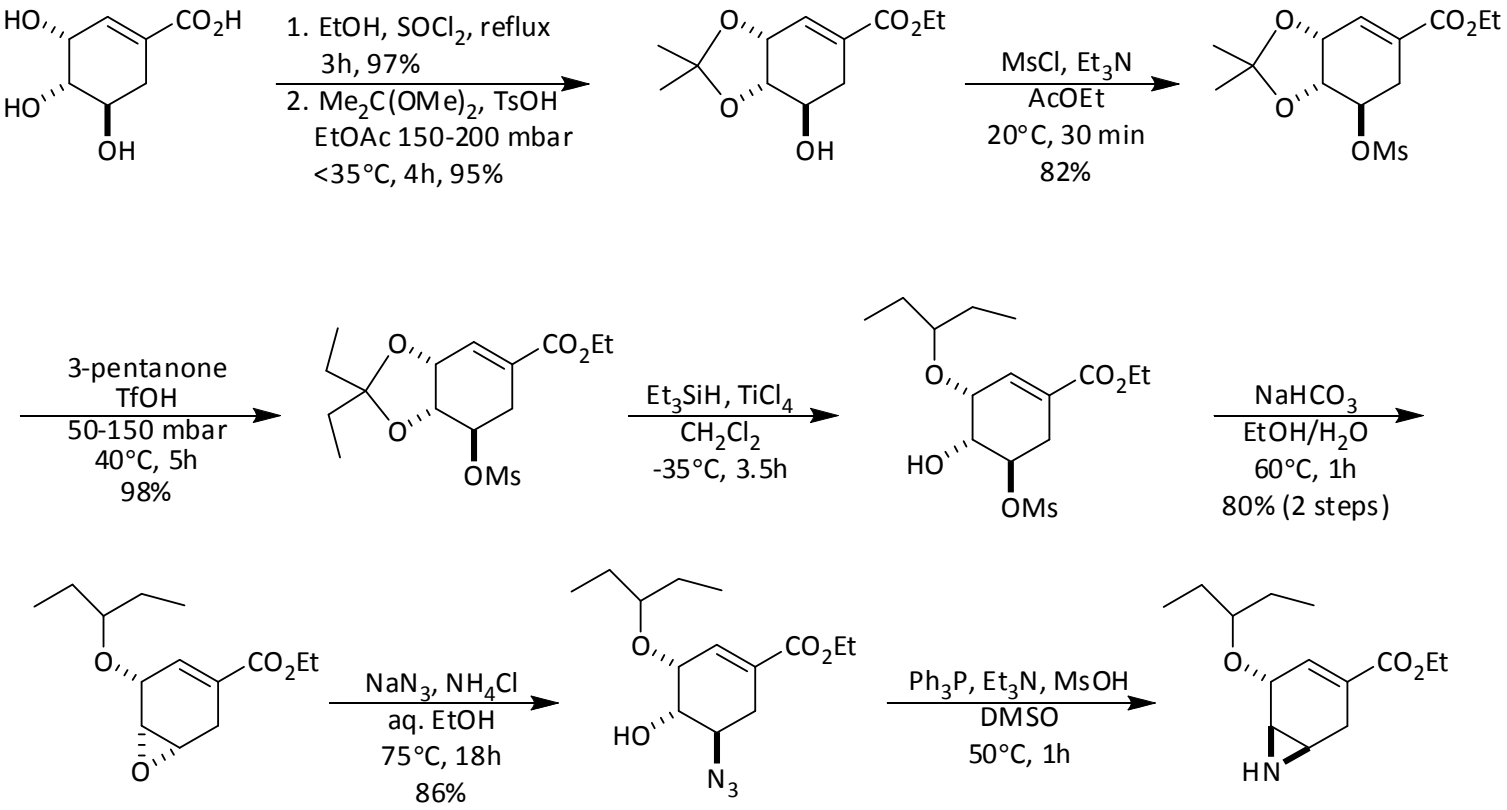



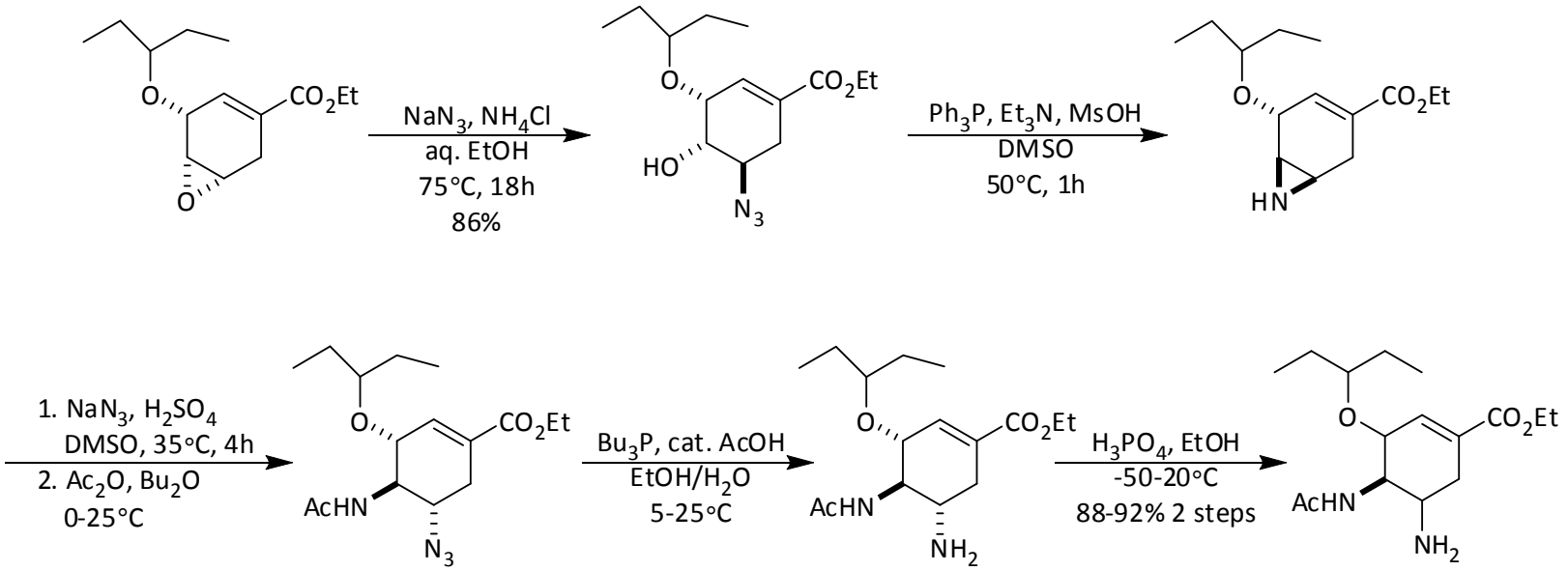
# Gilead Sciences – NA Inhibitor



# Roche's Synthesis



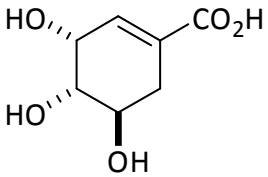
# Roche's Synthesis



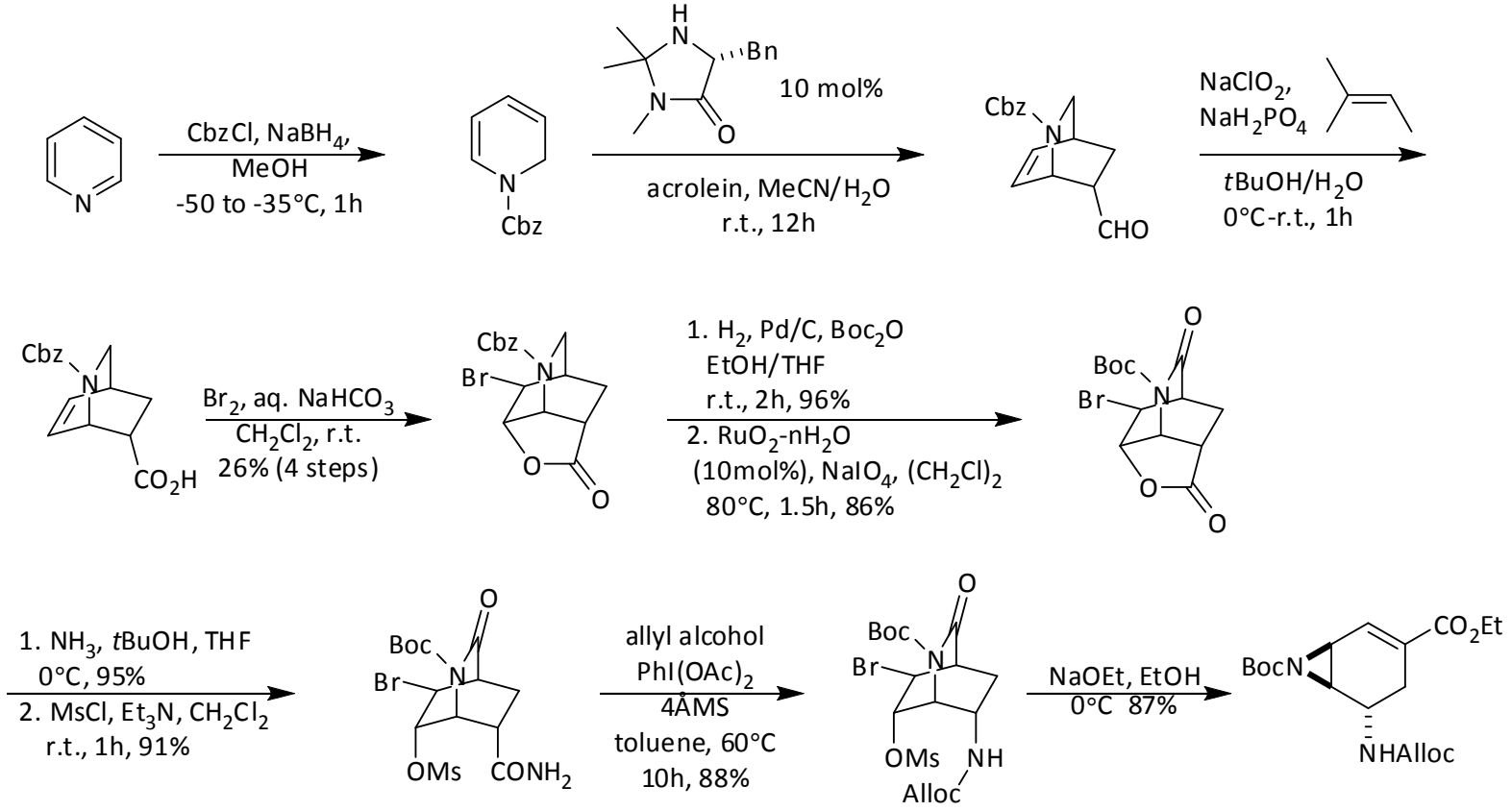

35-38% overall yield
12 steps

# Tamiflu on a Tonne Scale?

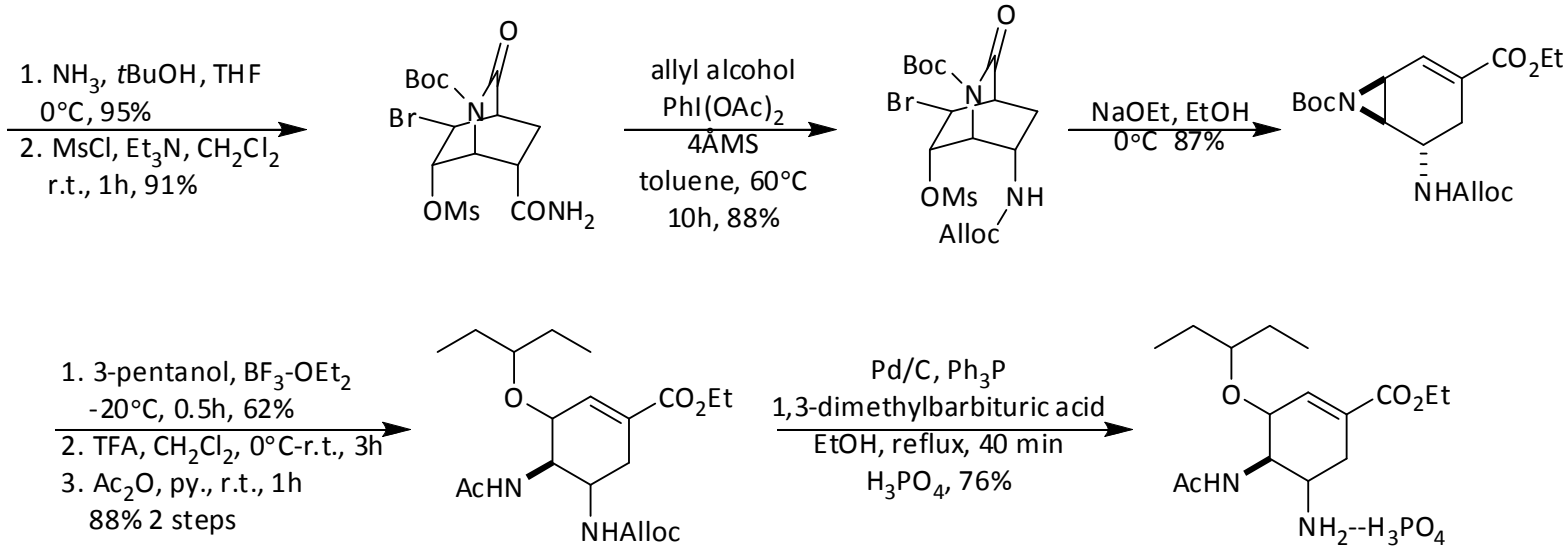
- The current public health opinion is that stockpiling Tamiflu is the only safeguard against an influenza epidemic.
- Issues:
  - Dosing – 75 mg dose – stockpiling could require on the order of millions of tonnes of Tamiflu
  - Availability of Shikimic Acid (1Kg from 30Kg dried Chinese star anise)
  - Dangers associated with azide chemistry
- Needed a synthesis from cheap, available starting materials.




# Tamiflu - Fukuyama



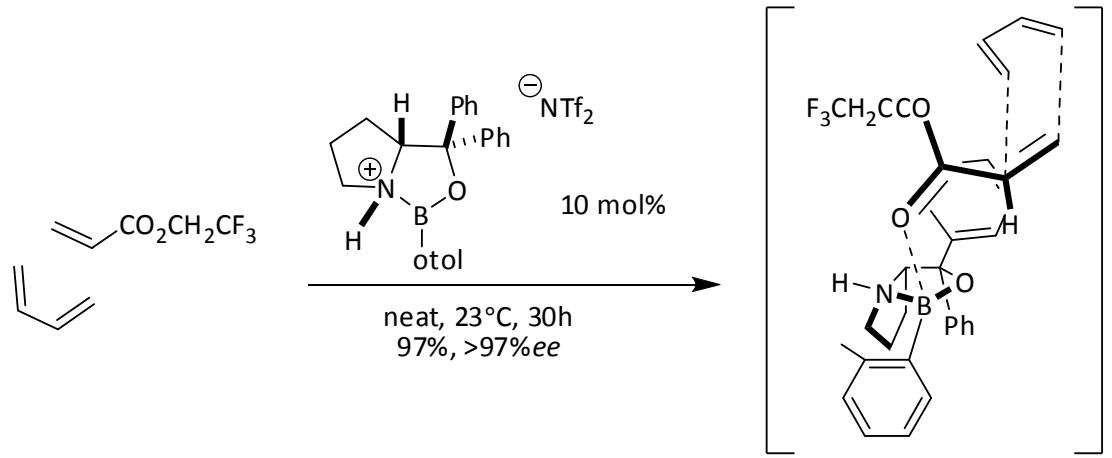
# Tamiflu - Fukuyama

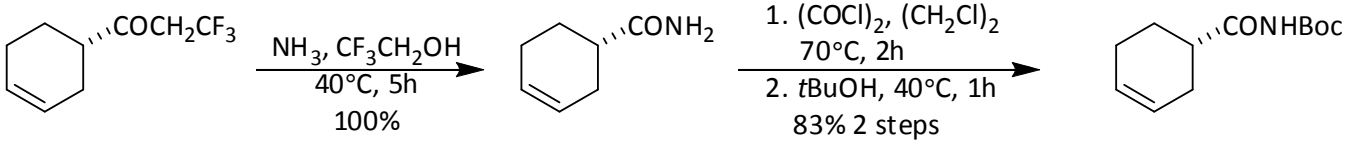


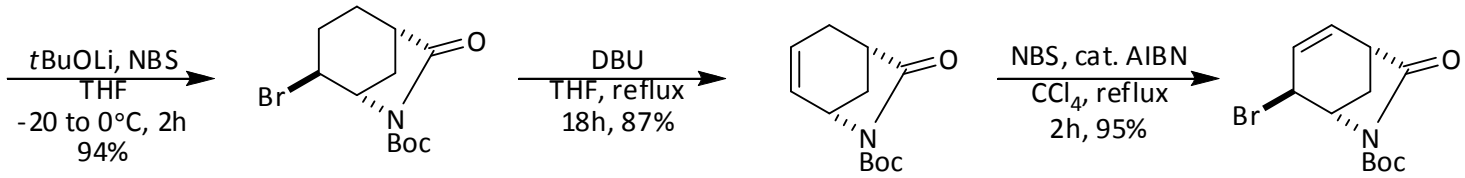

10% overall yield
14 total steps

- Azide free synthesis
- Commercially available starting materials
- Not Industrially useful overall yield

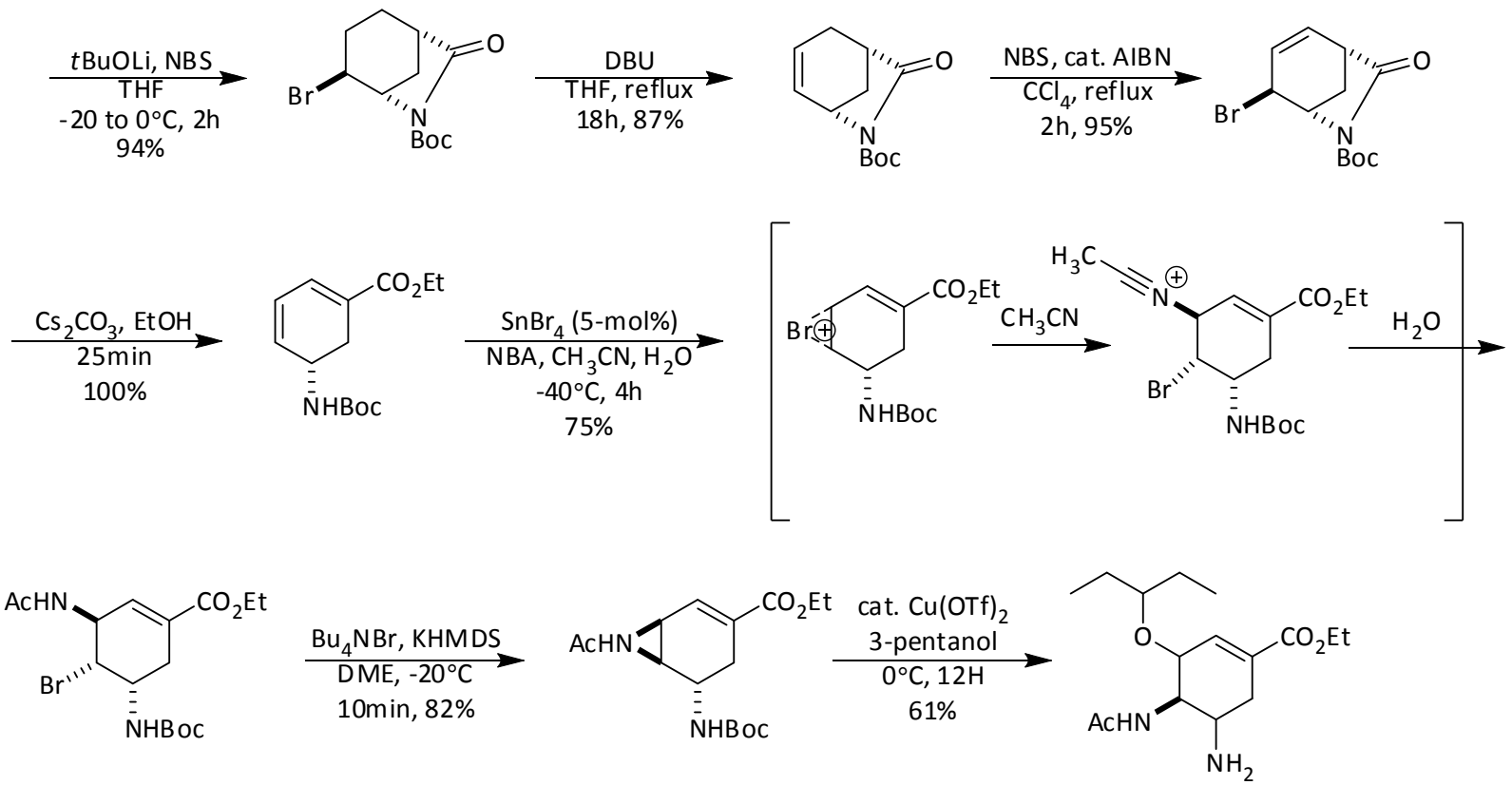
# Tamiflu – Corey



# Tamiflu – Corey



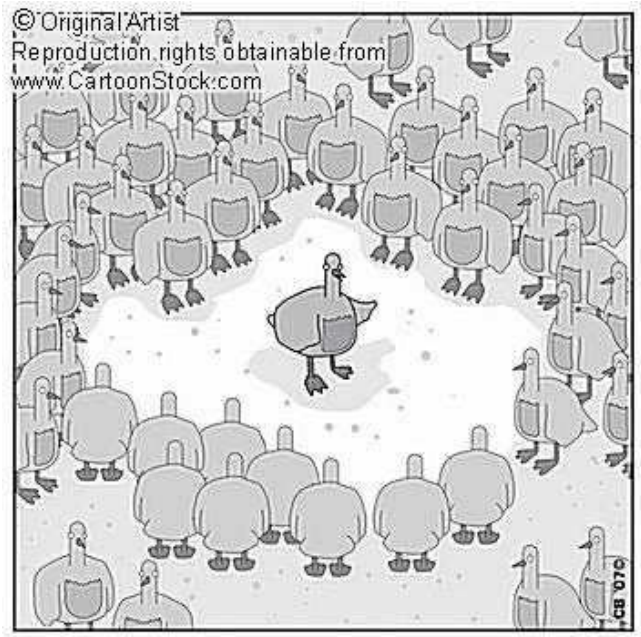

- Commercially available starting materials
- Azide free synthesis
- Potentially scalable

23% overall Yield
11 steps

# Other Notables

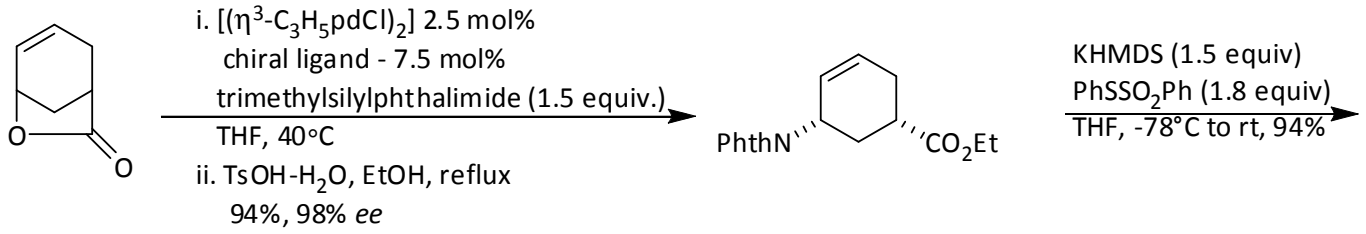
- Shibasaki – 3 generation synthesis.  Novel synthesis with PET imaging capability.
- Yao – begins with L-serine, but synthesis is too long.
- Kann – iron carbonyl complex sets chirality
- Fang – Analogues of Tamiflu

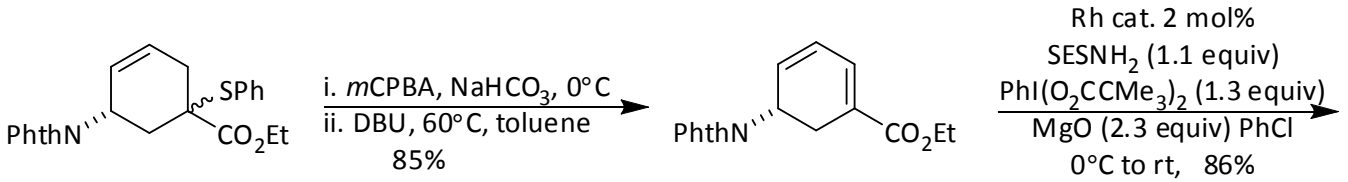
- Recently two syntheses
  - Trost
  - Hayashi

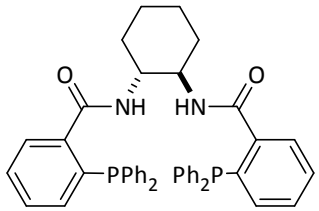



"No, no, no. I said the bird flew.
F - L - E - W"

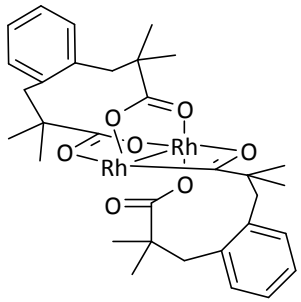
# Tamiflu – Trost



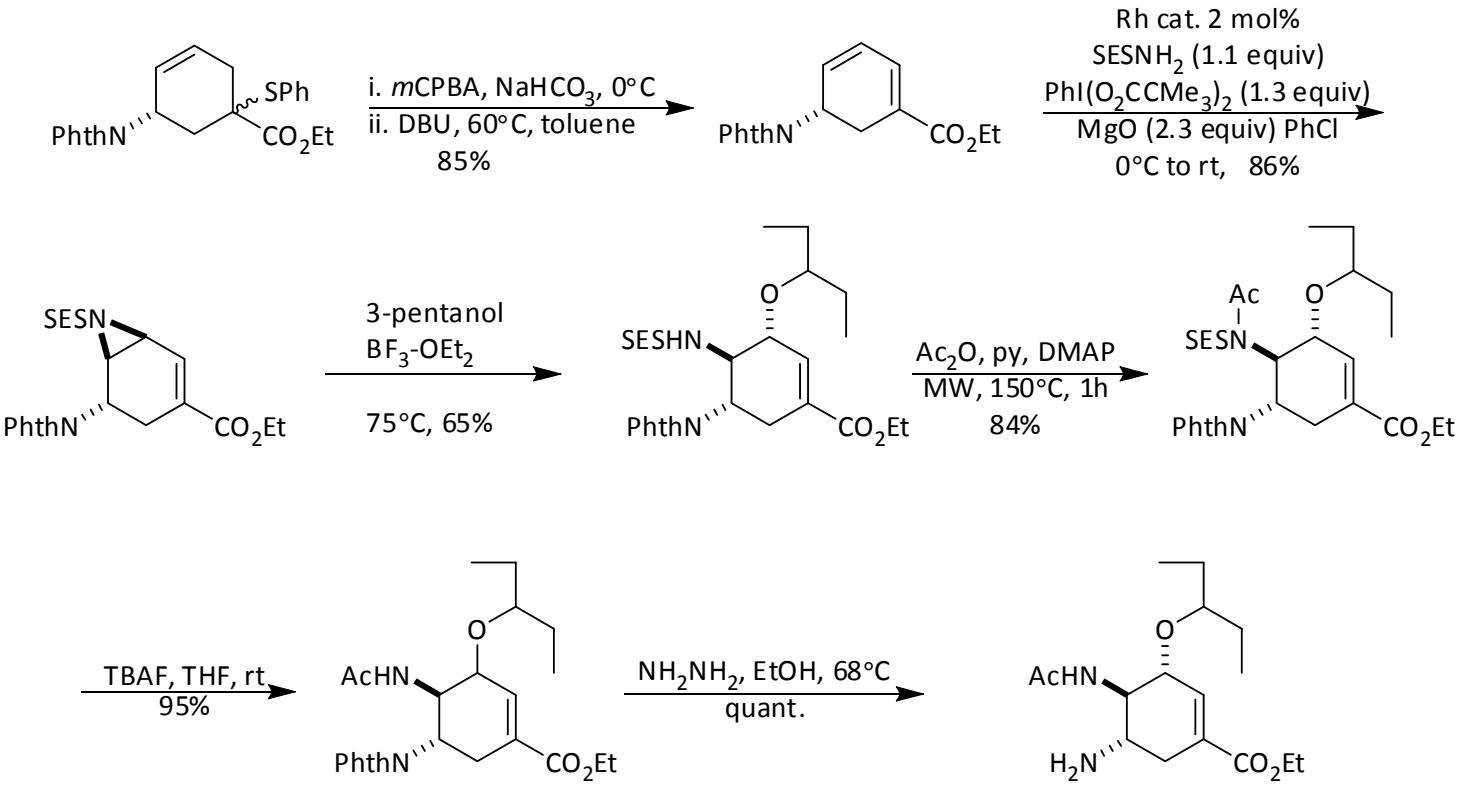




(*R*,*R*)



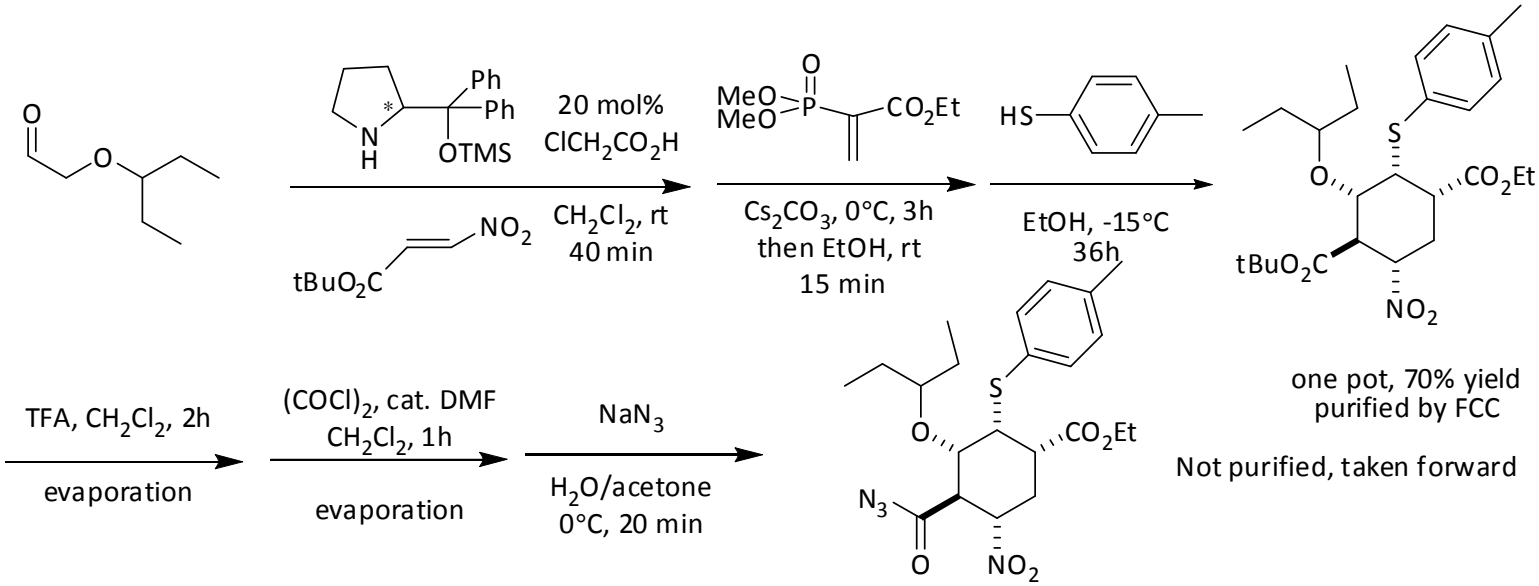
# Tamiflu – Trost

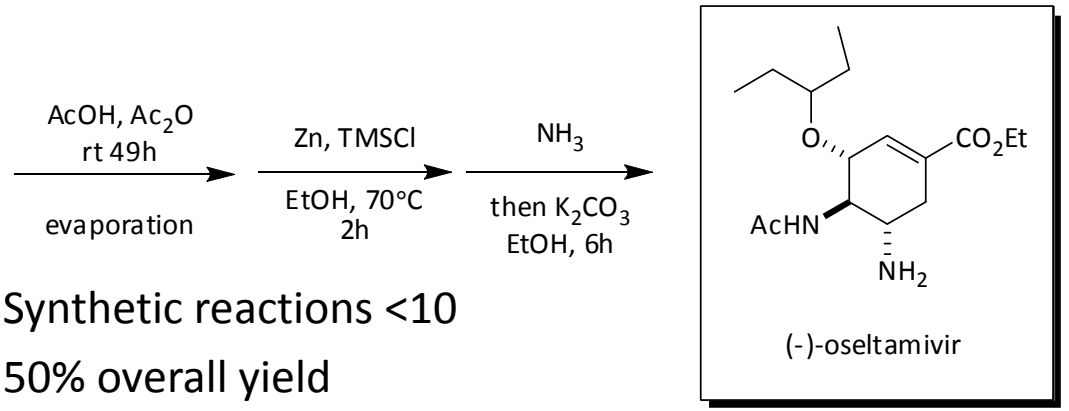



30% overall yield
8 total steps

- Commercially available starting material, azide free synthesis
- 8 total step count with higher overall yield

# Tamiflu - Hayashi




57% Overall yield
3 one-pot steps
2 purifications

- Synthetic reactions <10
- 50% overall yield
- Only inexpensive reagents

# Conclusions

- Current industrial syntheses yield approximately 30-33% overall.
- Many syntheses have been completed – the best syntheses around 30% overall yield, with the exception of Hayashi's synthesis.
- Tamiflu as a broad spectrum influenza neuroaminidase inhibitor is possible, though drug resistance is to be expected over time.


Gilead – JACS **1997**, 119, 681
Roche –JOC **1998**, 63, 4545
Corey – JACS **2006,** 128, 6310
Fukuyama – ACIEE **2007**, 46, 5734
Trost – ACIEE **2008,** 47, 3759.
Hayashi – ACIEE, ASAP **2009**
Review - *Eur. J. Org. Chem.* **2008**, 1839-1850