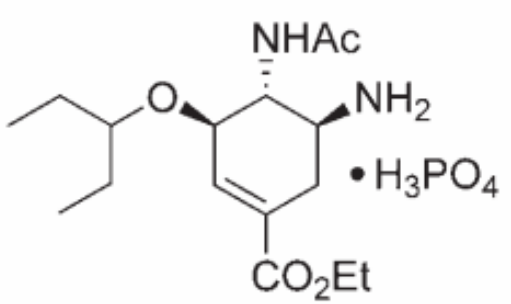
Current literature
July, 28th 2007
Filip Petronijevic

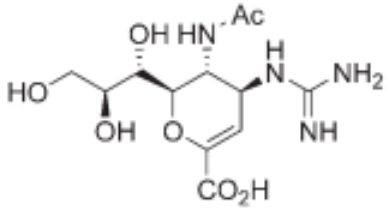


A Practical Synthesis of (-)-Oseltamivir

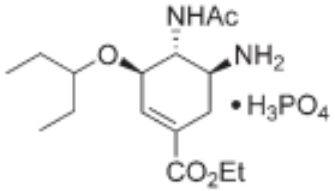
Nabuhiro Satoh, Takahiro Akiba, Satoshi Yokoshima, Thoru Fukuyama

Angew. Chem. Int. Ed. **2007**, *46*, 5734.

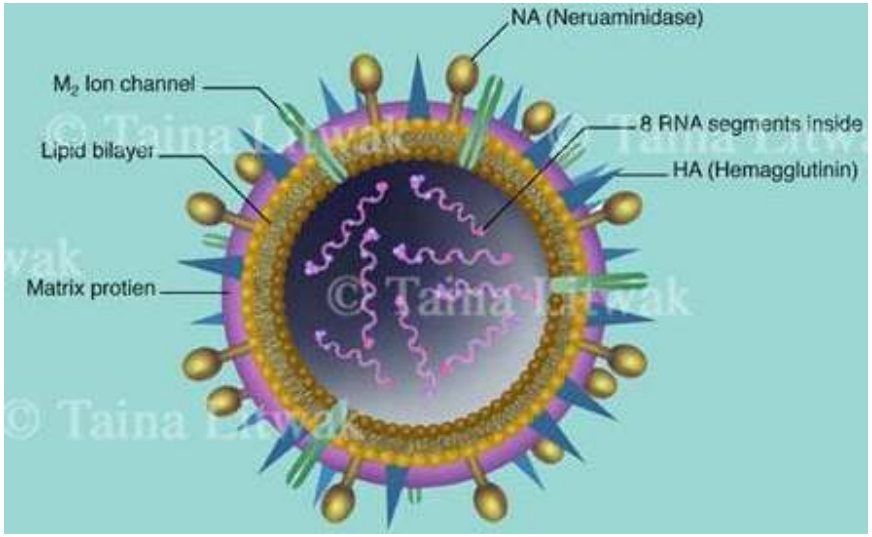
Against Influenza

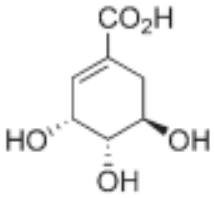


1

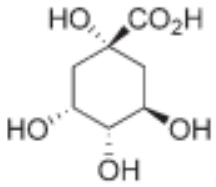


2





3



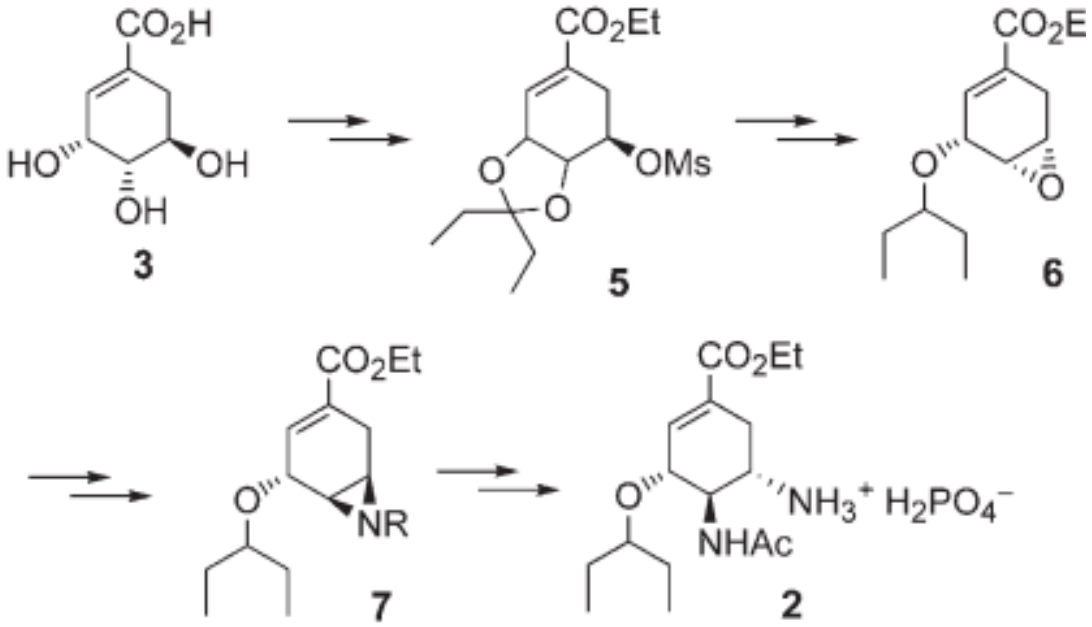
4

3 shikimic acid
4 quinic acid

1 zanamivir (Relenza)
2 oseltamivir phosphate (Tamiflu)

- The avian H5N1 influenza shows a lethality rate of over 50%
- Three types of influenza viruses (A, B and C) have different proteins
- Inhibitors of the M2 protein (amantadine and rimantadine) show side effects
- Zanamivir causes respiratory problems in some cases
- Oseltamivir is a prodrug and acts on NA

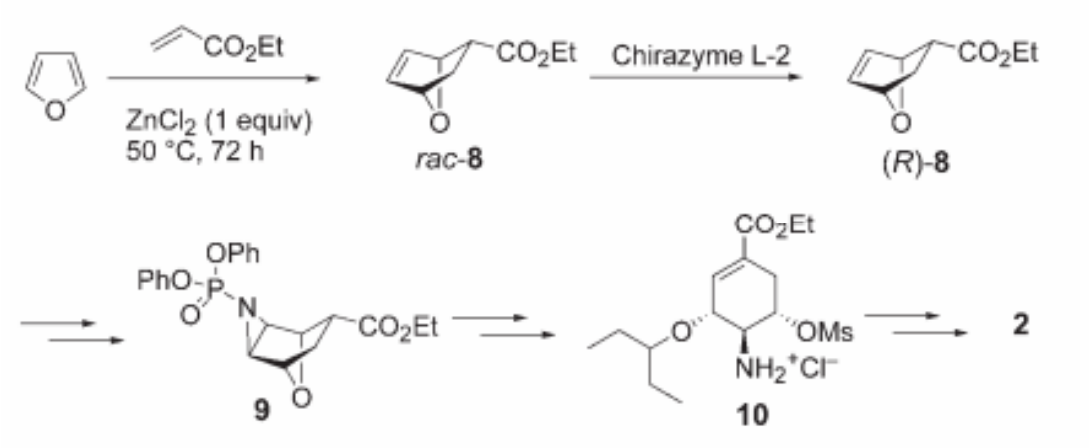
The First Generation Approach to Tamiflu



"The dependence on using azide chemistry to convert epoxide **6** into oseltamivir phosphate was considered a weakness in the first-generation manufacturing process"

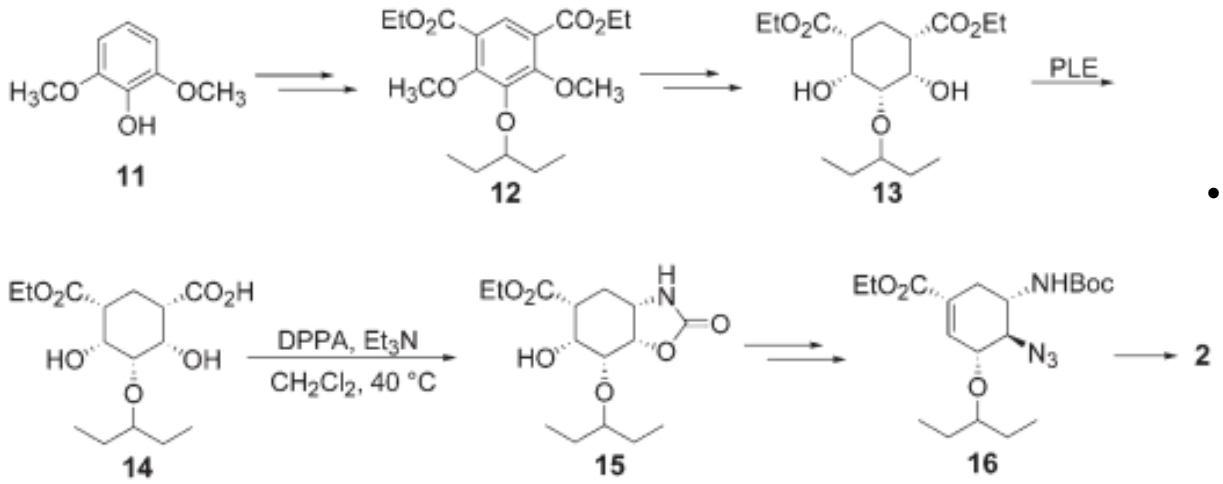
Angew. Chem. Int. Ed. **2006**, *45*, 7330.

The Second Generation Approach to Tamiflu



- several steps require high dillution
- low yield (20%) of the enzymatic resolution step

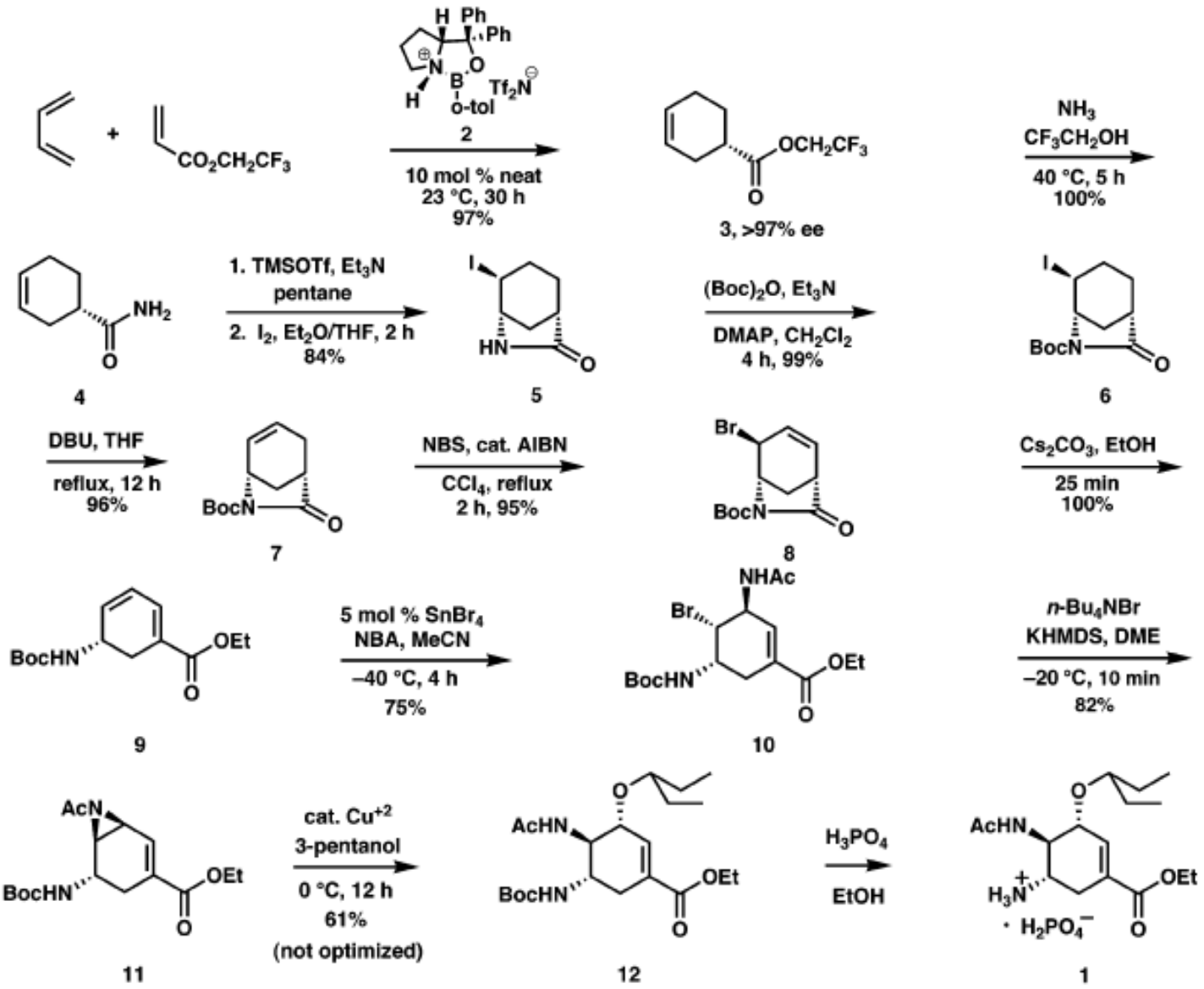
The Third Generation Approach to Tamiflu



- "… it still uses sodium azide.. "

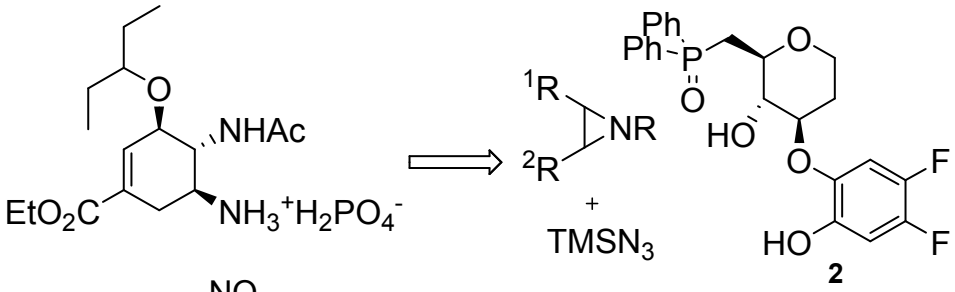
Angew. Chem. Int. Ed. **2006**, *45*, 7330.
J. Org. Chem. **2001**, *66*, 2044.

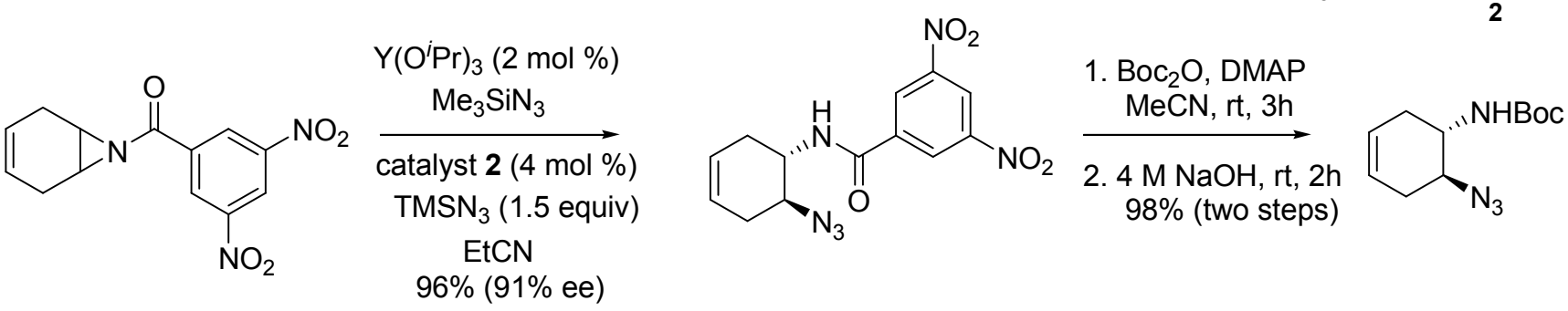
Corey's Approach: The approach features a highly enantioselective and high-yielding cycloaddition promoted by a catalytic amount of oxazaborolidine

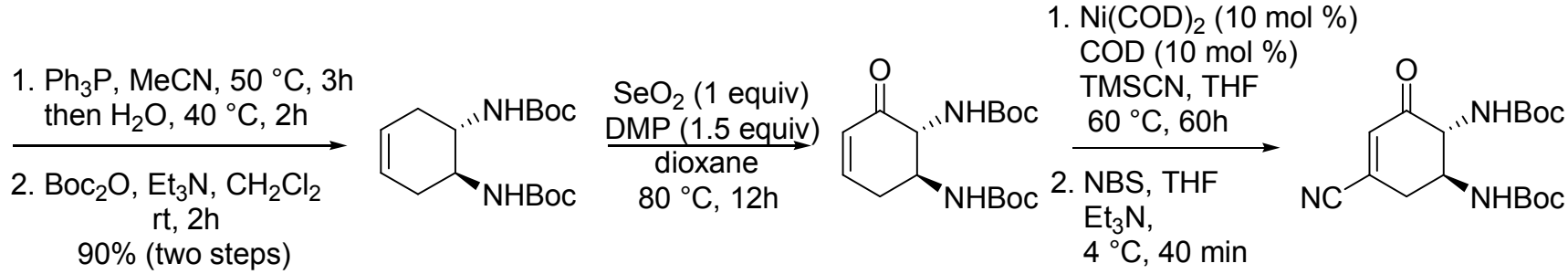


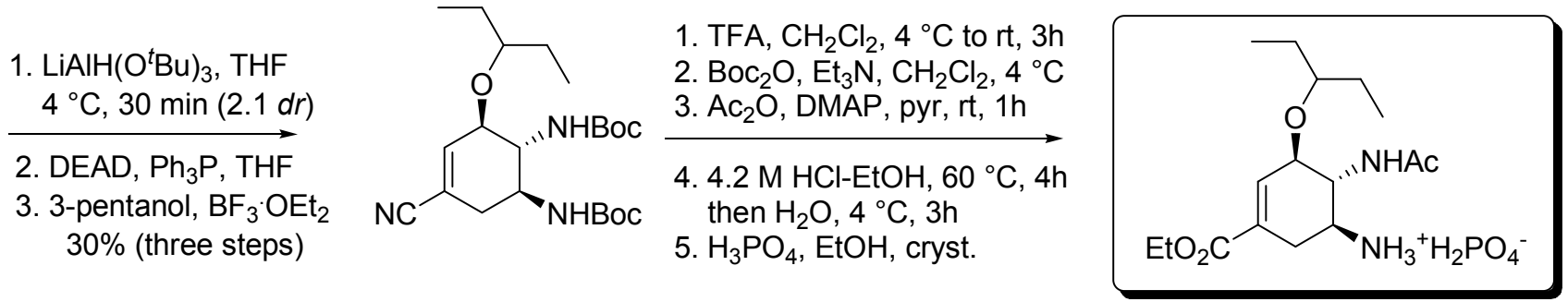
J. Amer. Chem. Soc. **2006**, *128*, 6310

Shibasaki's First Approach



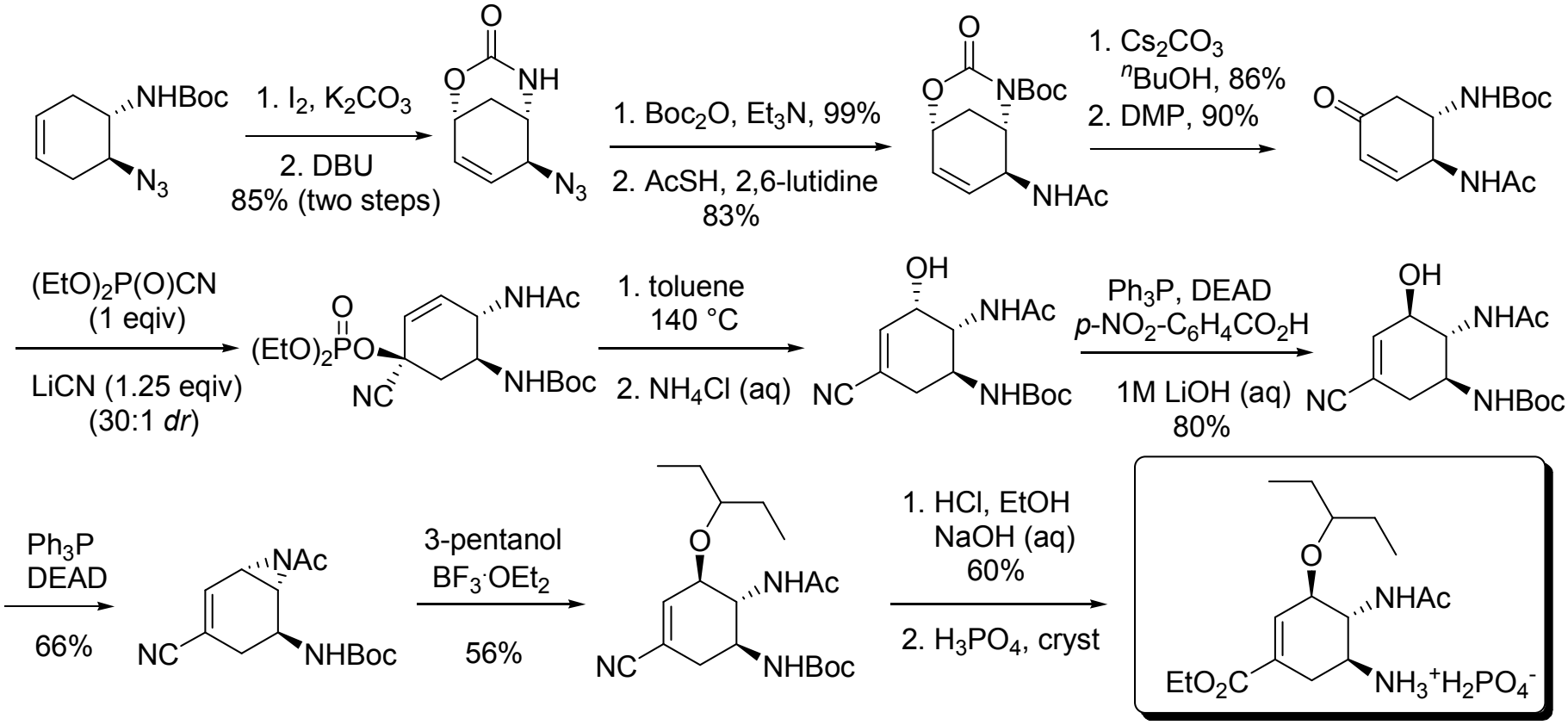






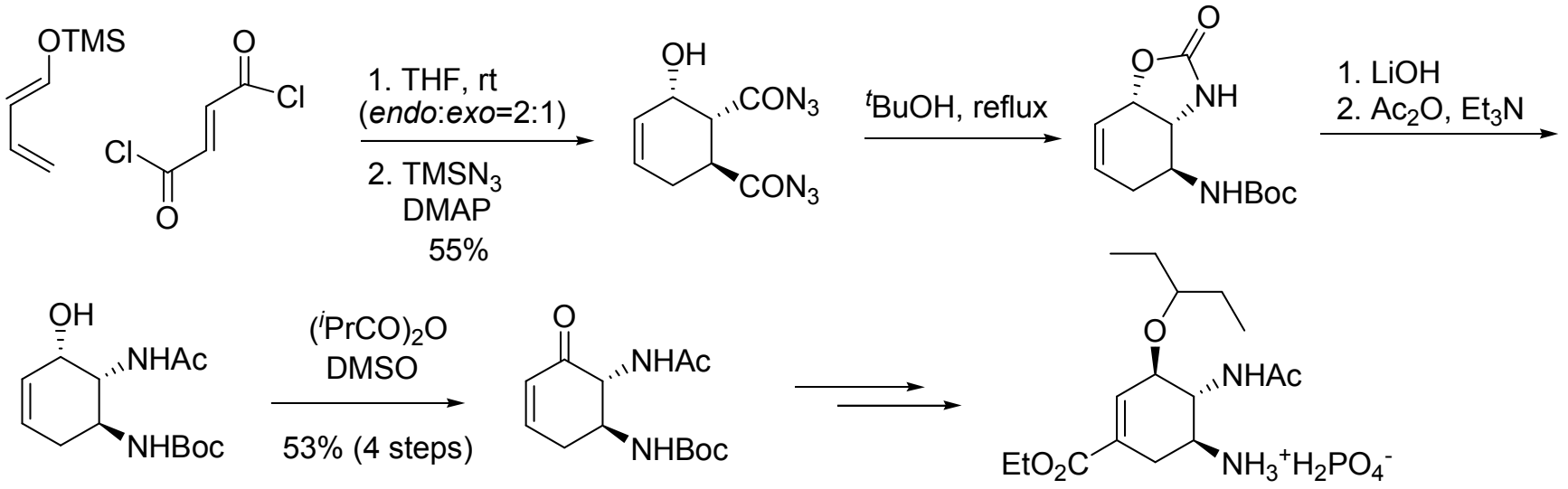
J. Amer. Chem. Soc. **2006**, *128*, 6312.

Shibasaki's Second Approach



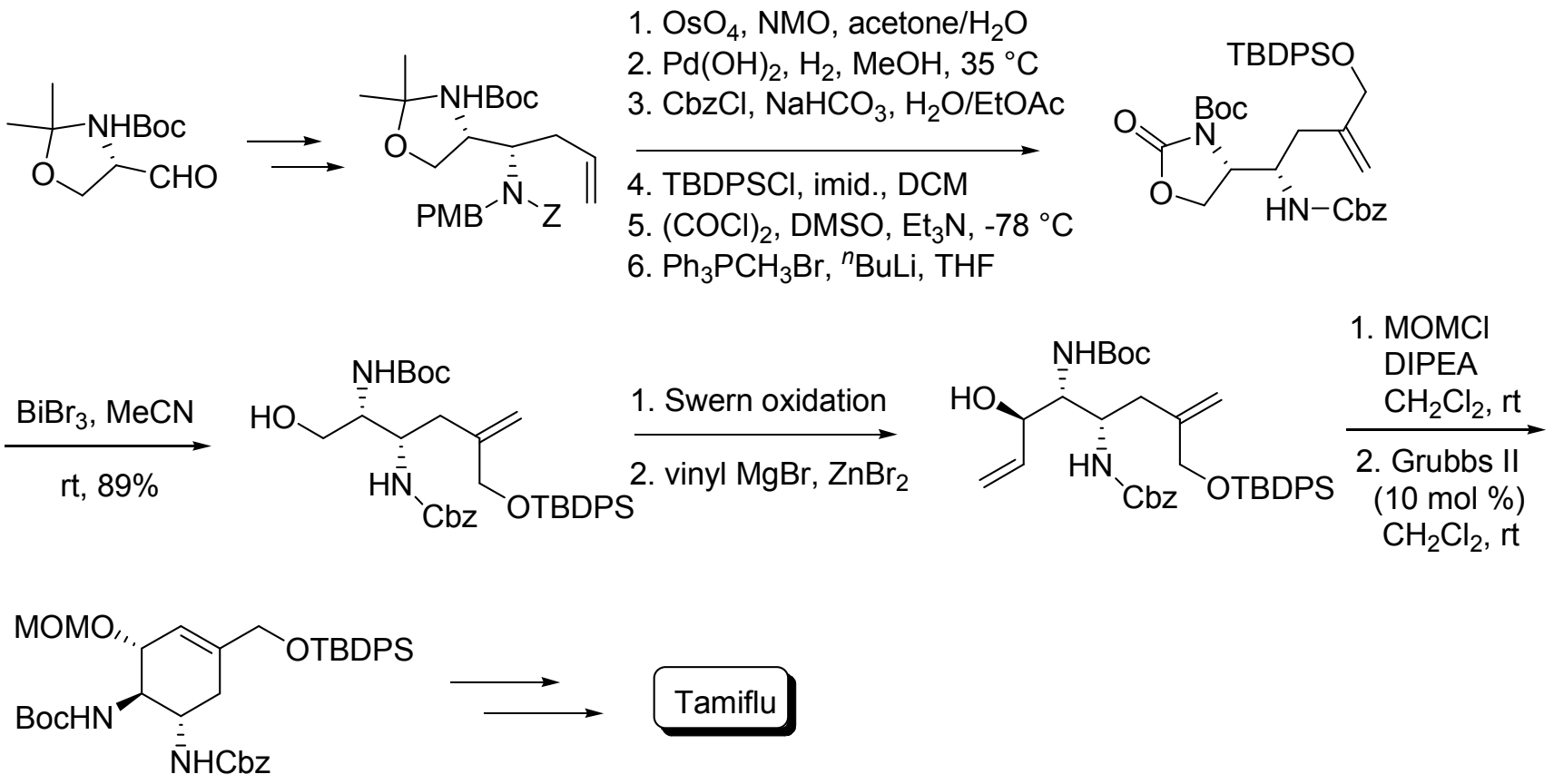
Org. Lett. **2007**, *9(2)*, 259.

Shibasaki's Third Synthesis



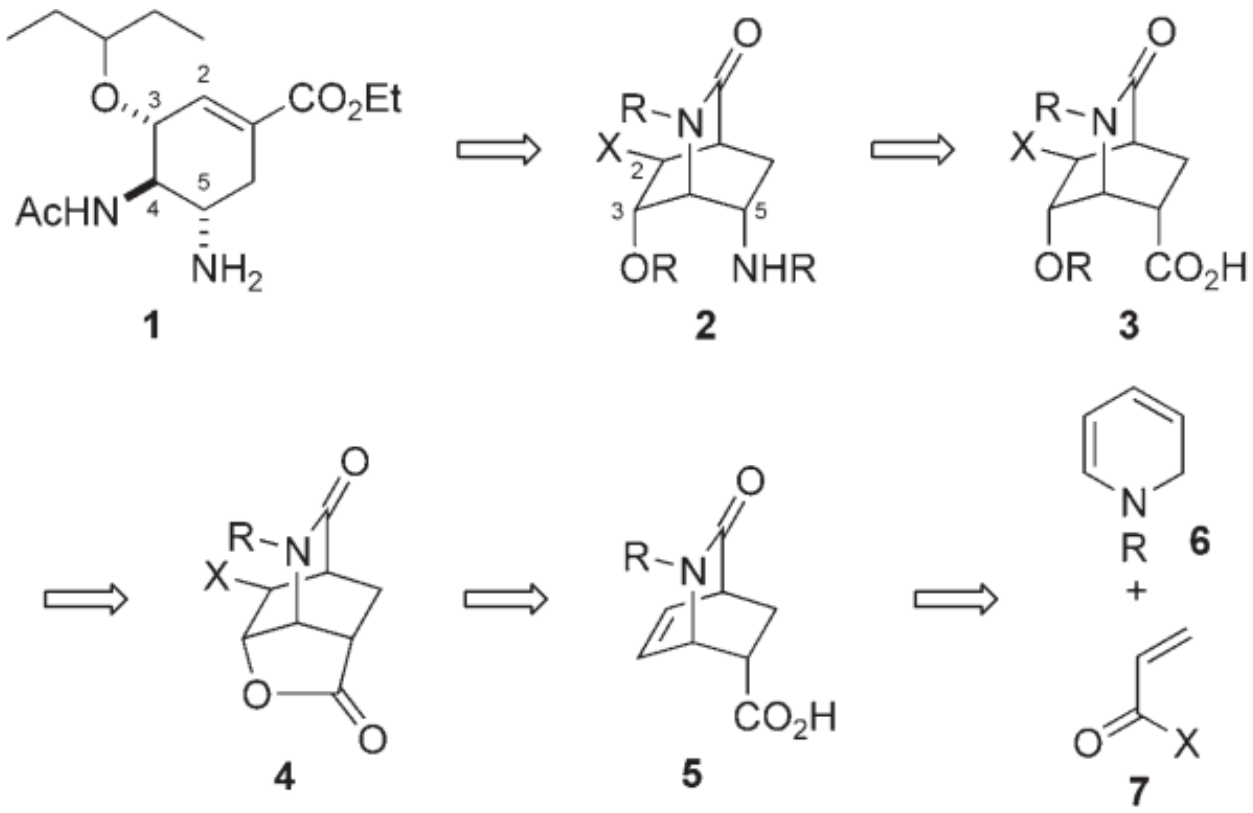
Tet. Lett. **2007**, *48*, 1403.

Cong and Yao's Approach: The synthesis is based on a ring-closing metathesis reaction, catalyzed by second-generation Ru carbene catalyst



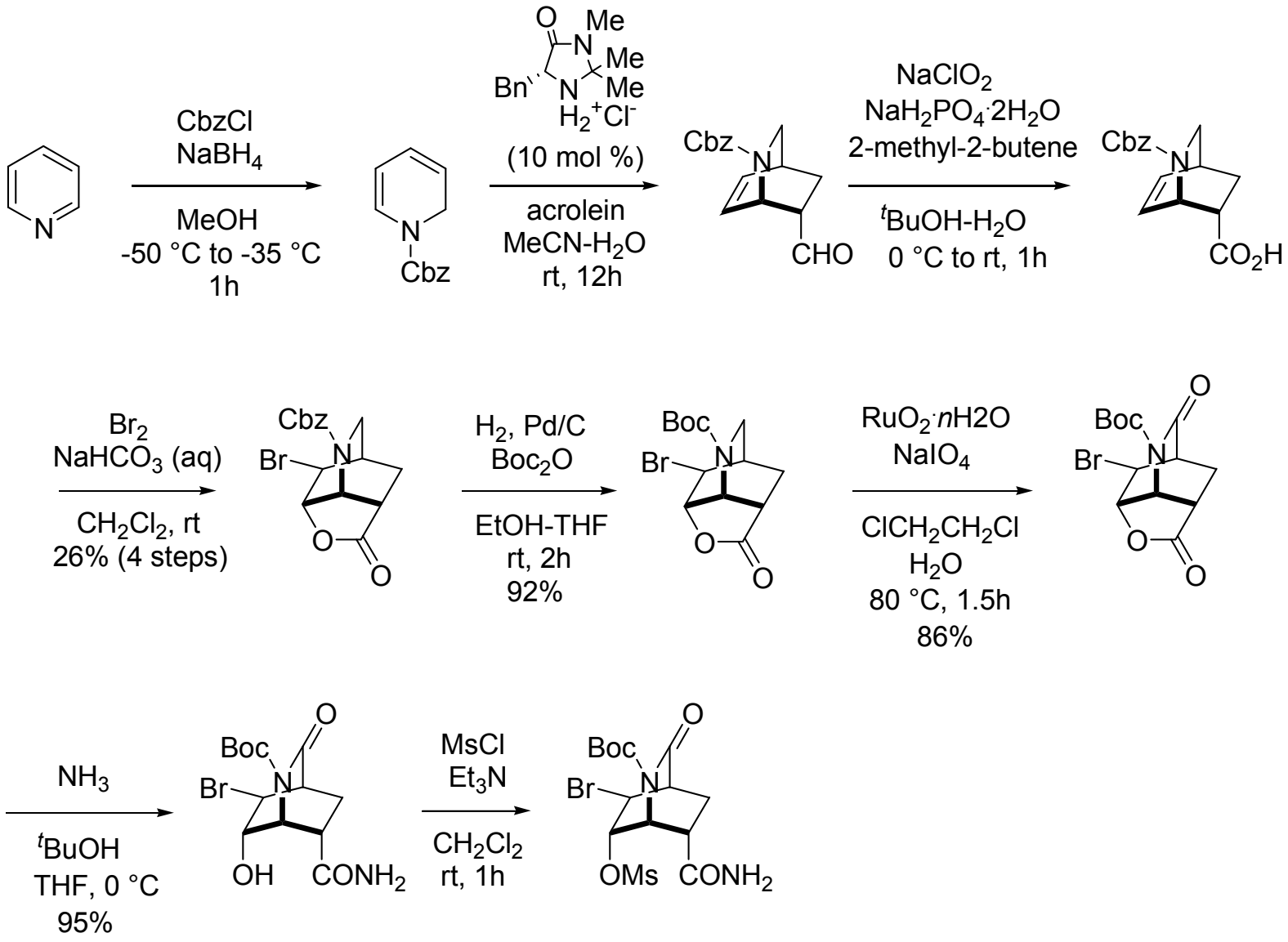
J. Org. Chem. **2006**, *71*, 5365.
J. Org. Chem. **2004**, *69*, 5314.

Fukuyama's Synthesis: Retrosynthetic Analysis



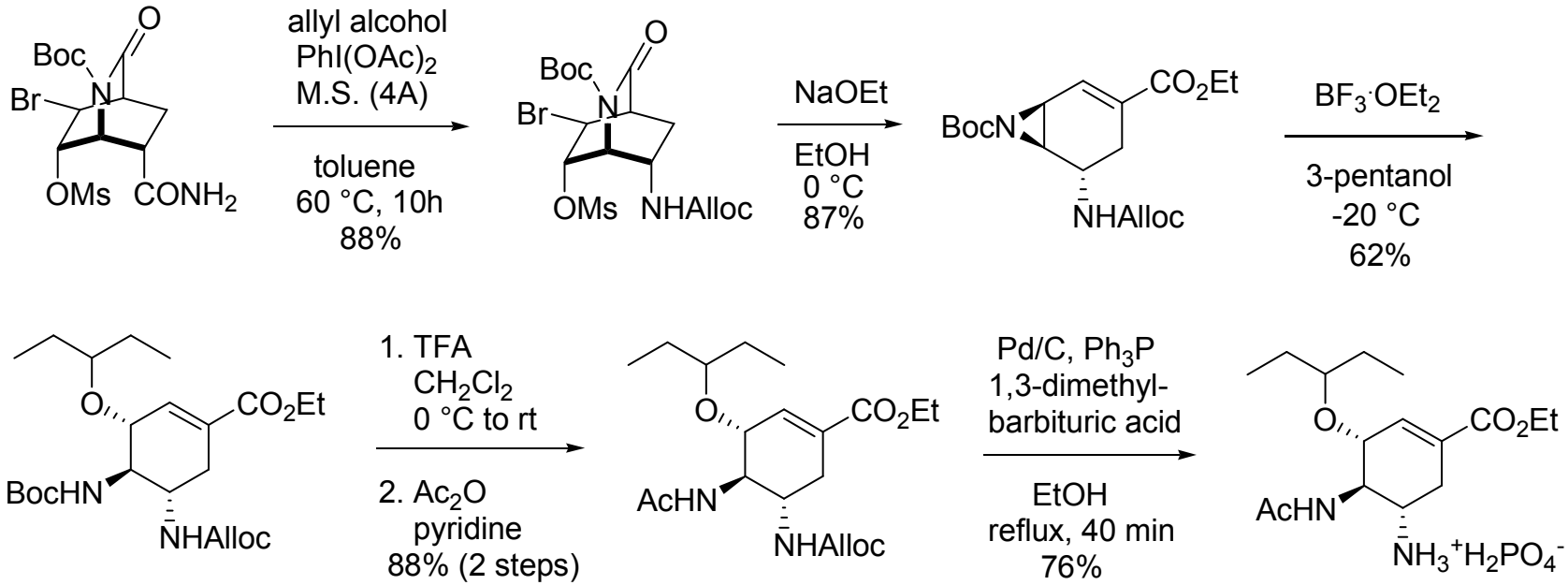
Angew. Chem. Int. Ed. **2007**, *46*, 5734.

Fukuyama's Synthesis: The Asymmetric Diels-Alder Reaction in Action



Angew. Chem. Int. Ed. **2007**, *46*, 5734.

Fukuyama's synthesis: The End



Angew. Chem. Int. Ed. **2007**, *46*, 5734.

Conclusions

- inexpensive and commonly used reagents are employed
- the overall yield of lactone from benzyl chloroformate is rather low (26%) this intermediate can be obtained easily with no tedious purification
- the other reactions proceed in high yields
- oseltamivir phosphate is obtained in 5.6% yield from benzyl chloroformate by using an asymmetric DA reaction and a Hoffman rearrangement as key transformations
- this synthesis uses an easily available starting material compared to the current industrial Roche synthesis in which shikimic acid is employed as precursor
- this route is has great potential for tamiflu analogues syntheses