

Tamiflu

(Oseltamivir Phosphate)

Molecule in Review

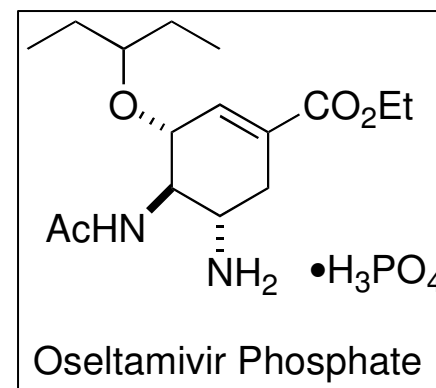
Lisa Ambrosini
Lambert Group
August 14, 2009

Synthesis Literacy Group
Columbia University Chemistry



Tamiflu

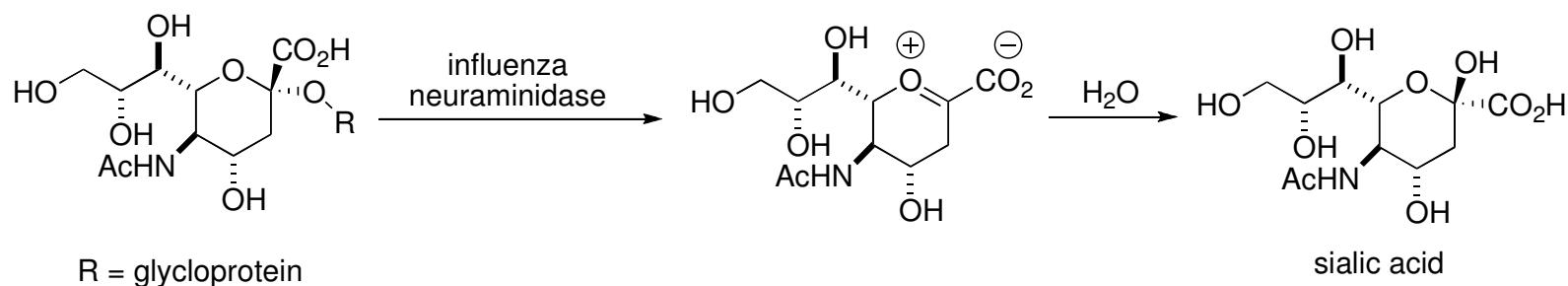
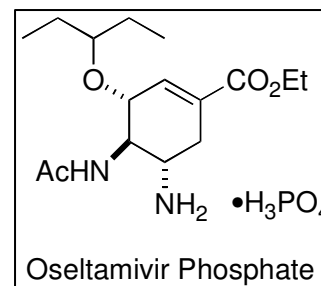
- Influenza
 - Seasonal
 - Avian
 - Swine
- Discovered at Gilead 1995
 - Codeveloped with Roche
 - Launched by Roche 1999
- 50 million people treated
 - \$2.1 billion in 2006
 - \$564 million in 2008
 - Predicted sales increase of 531%



QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Oseltamivir Phosphate

- Orally active neuraminidase inhibitor
 - Competitive inhibitor towards sialic acid
 - Designed as analogue of oxocarbenium intermed.
 - Prevents viral release and spread of disease

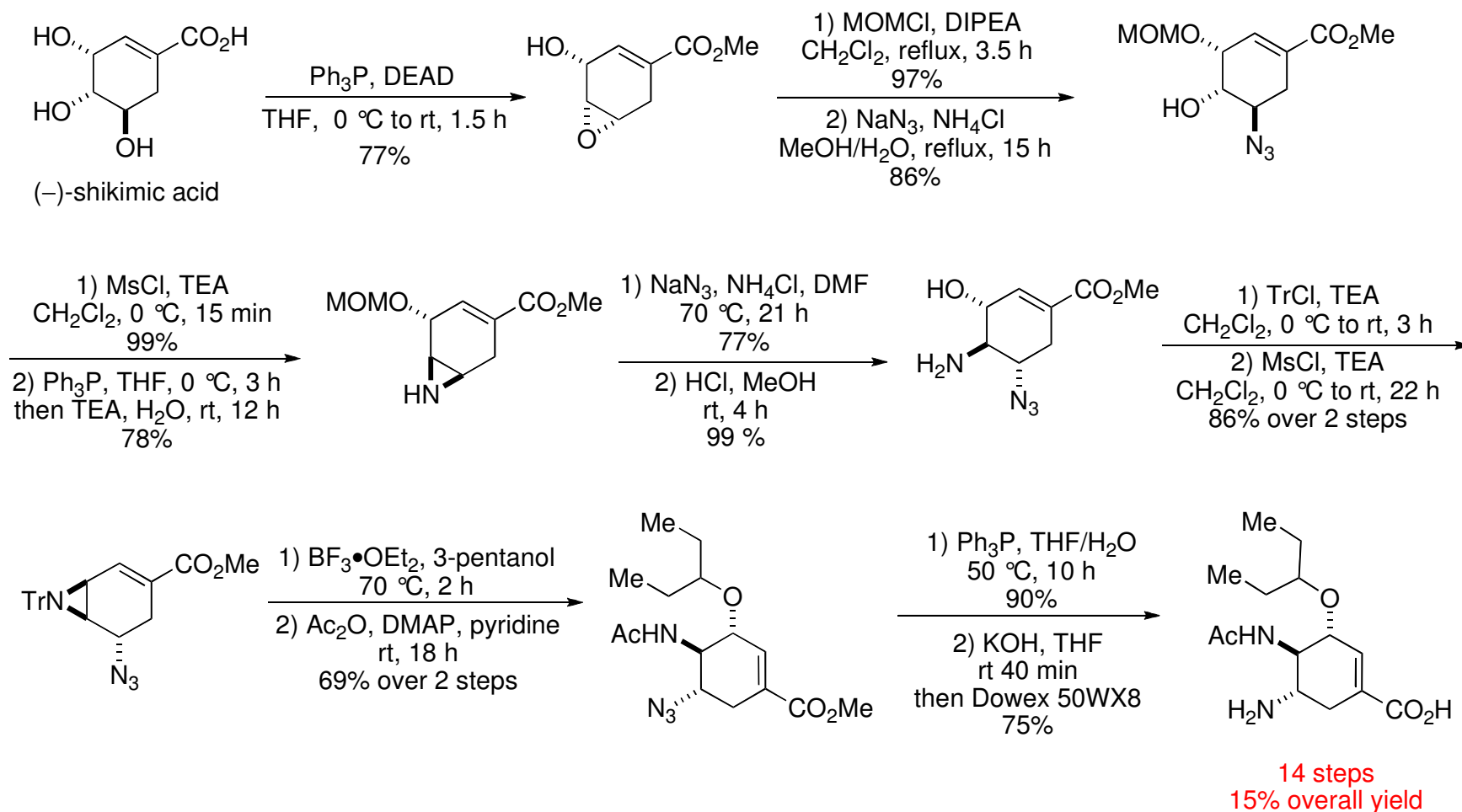


- Dose: 75 mg twice daily for 5 days
- 2010- production at 400 million packs per year

Synthesis of Tamiflu

- Nearly 30 published syntheses of molecule or intermediates
- First Synthesis by Gilead
- A process Route by Hoffmann-La Roche
- Inexpensive Route by Shibasaki
- Shortest Synthesis by Trost
- Highest Yielding Synthesis by Hayashi

First Synthesis- Gilead

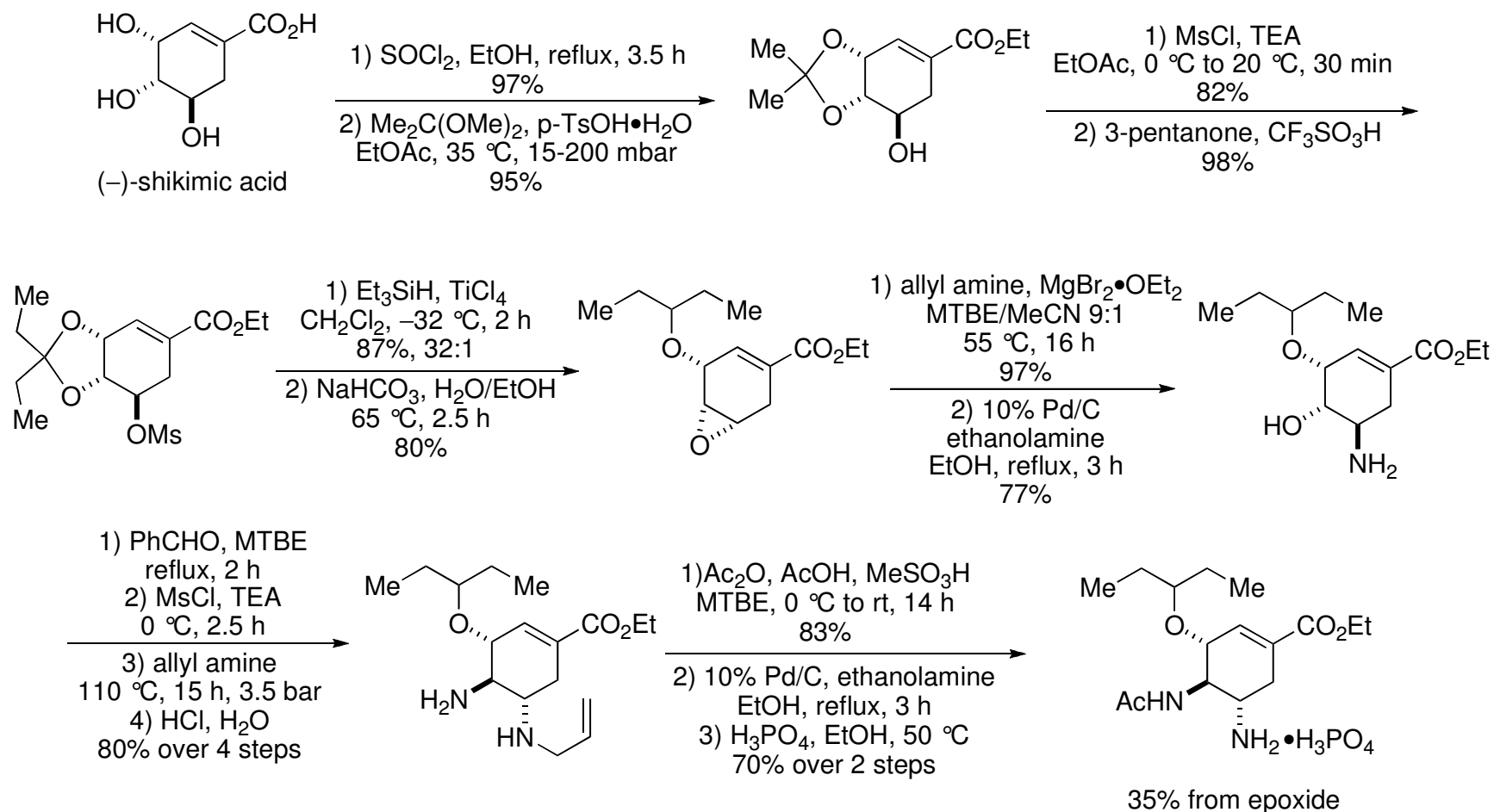


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First Synthesis- Gilead

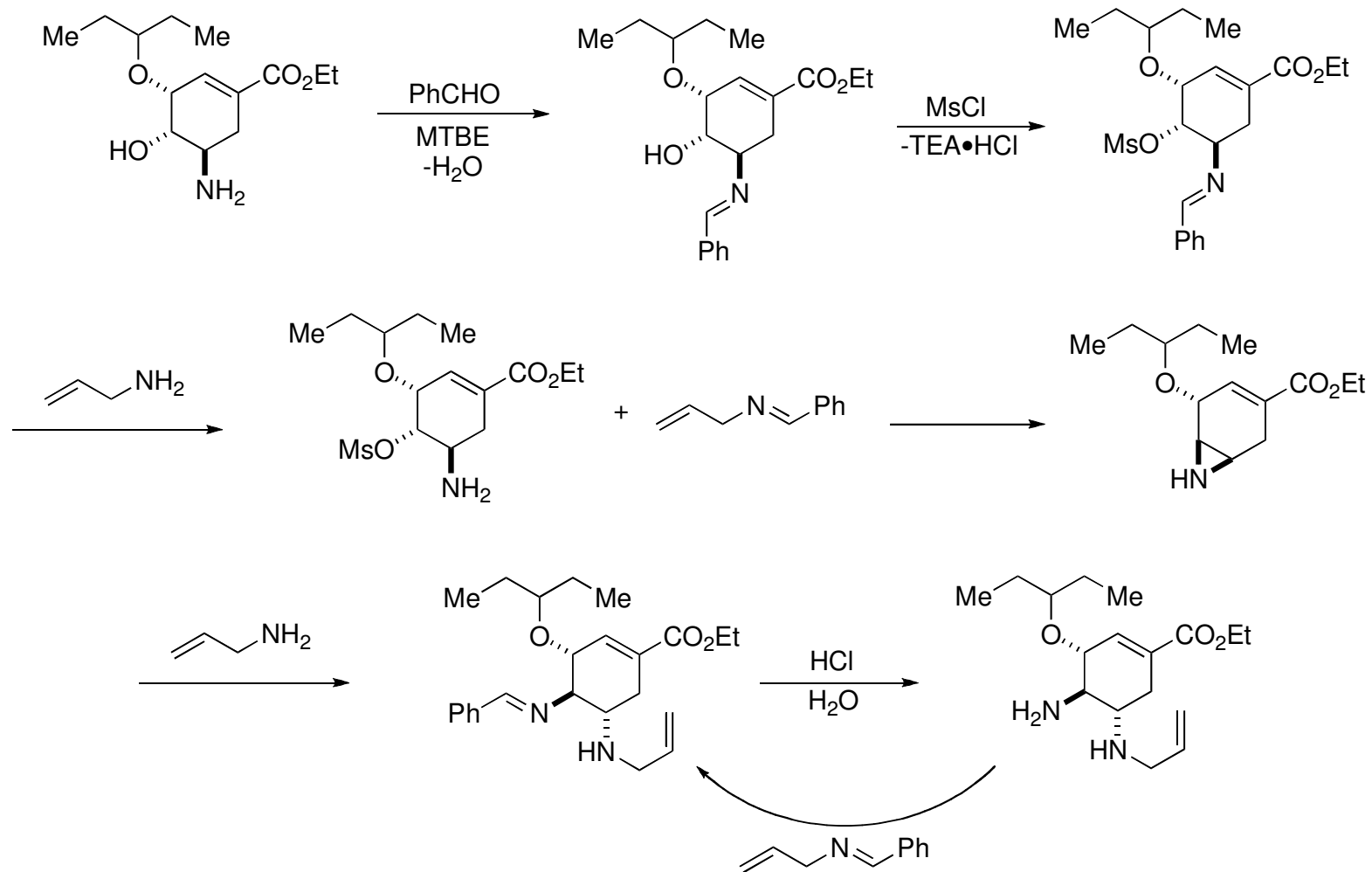
- Demonstrated on milligram scale as candidate molecule
- Uses shikimic acid as starting material
 - Isolated from Chinese star anise
 - Cannot be synthesized economically
- Uses azide chemistry (twice!)

Process Synthesis- Hoffmann-La Roche



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Process Synthesis- Hoffmann-La Roche



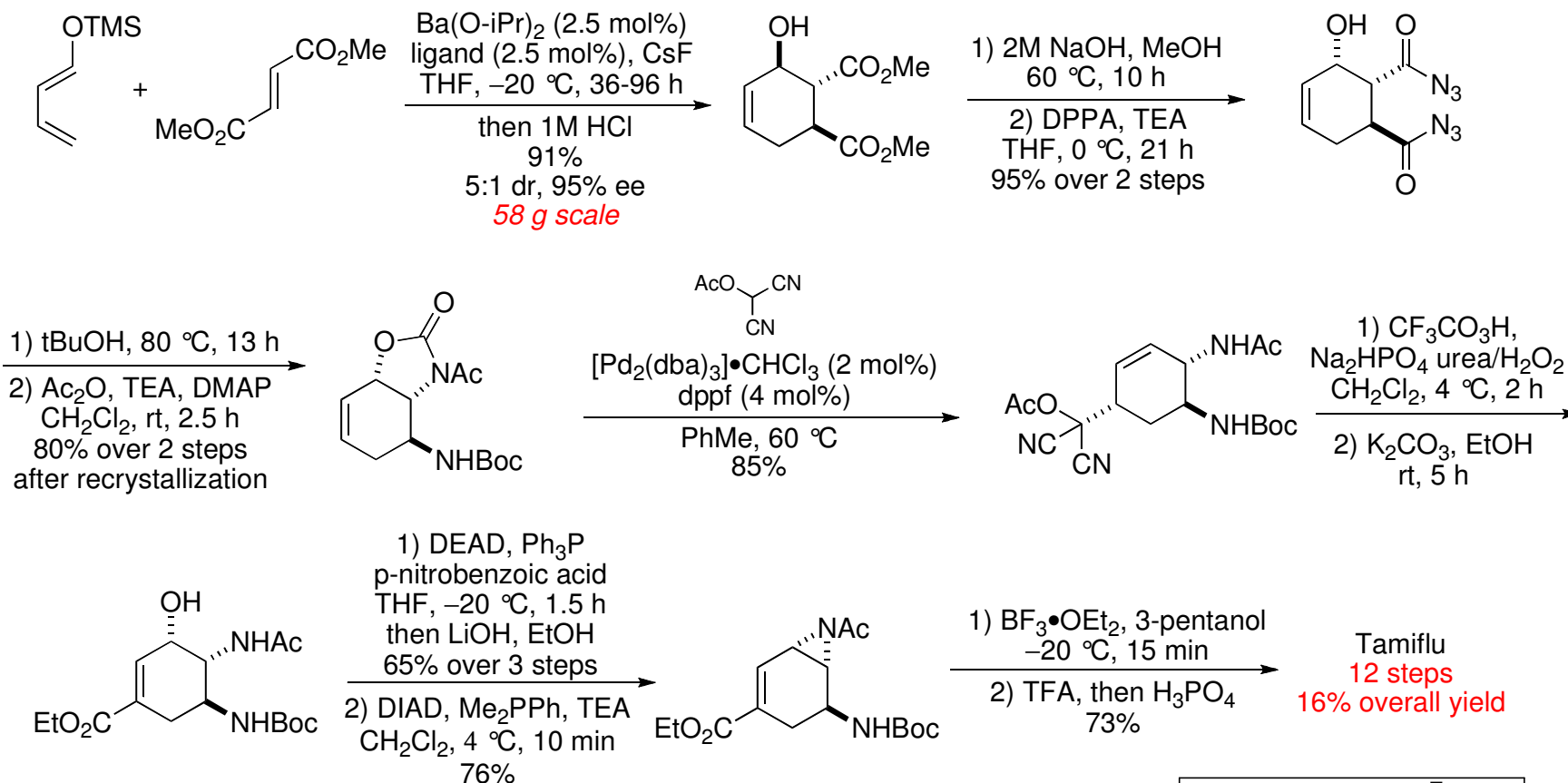
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Process Synthesis- Hoffmann-La Roche

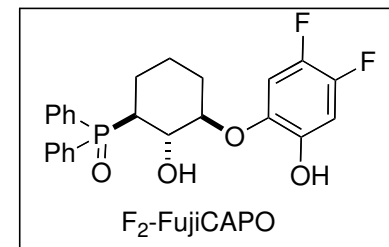
- 35% from epoxide
- Azide-free
- Avoids chromatography

- Uses shikimic acid as starting material
- Only demonstrated on multigram scale

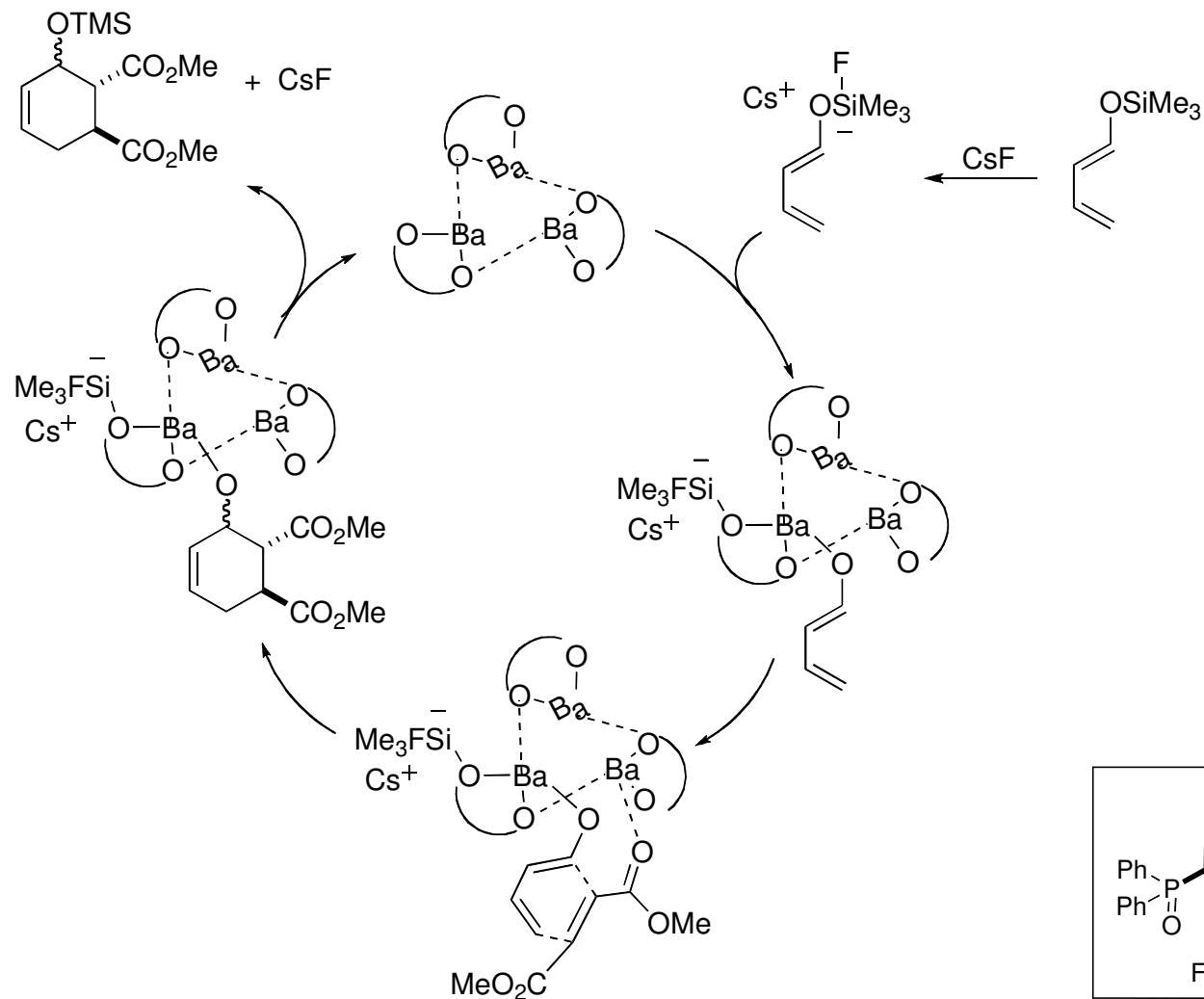
Shibasaki



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Shibasaki

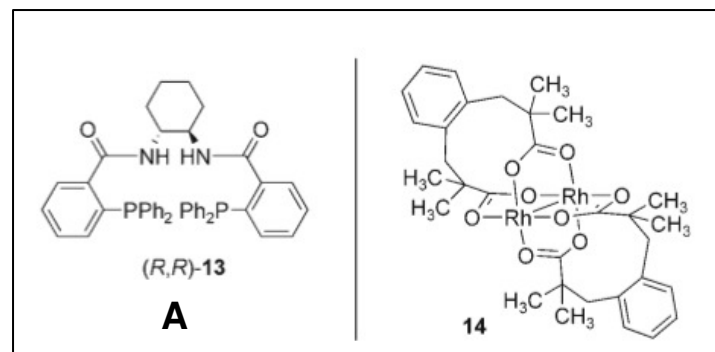
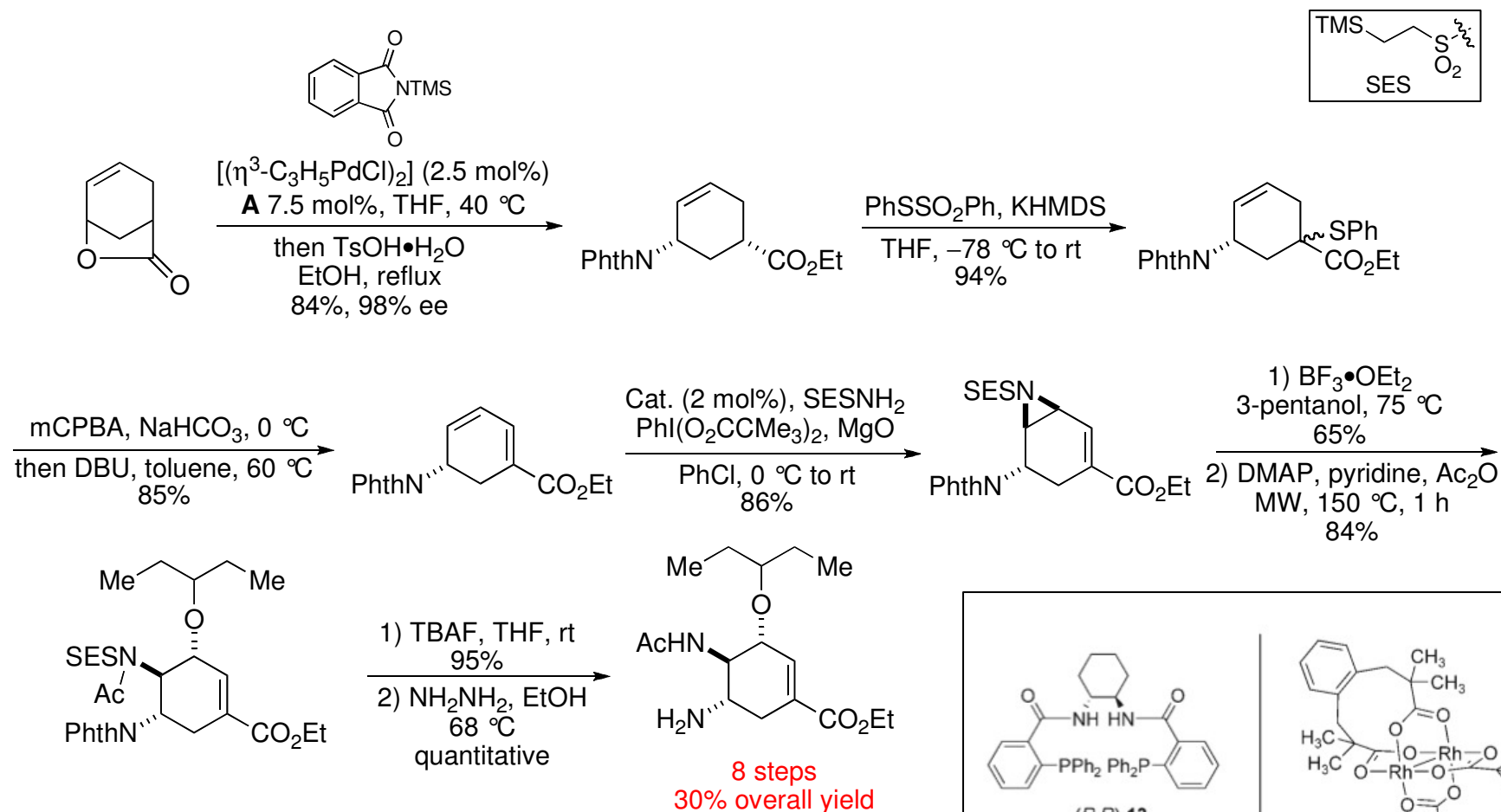


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Shibasaki

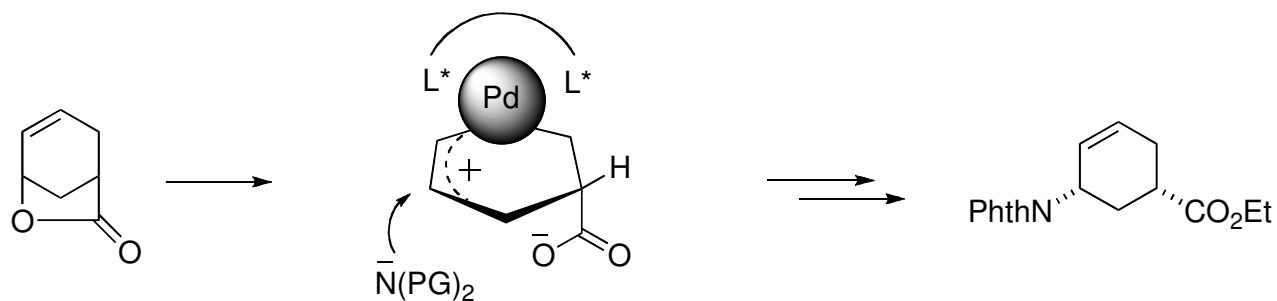
- 16% yield in 12 steps
 - Commercially available starting materials
 - Introduces chirality in first step
 - Scalable
-
- Uses azide chemistry
 - High temperature Curtius rearrangement

Shortest Route- Trost

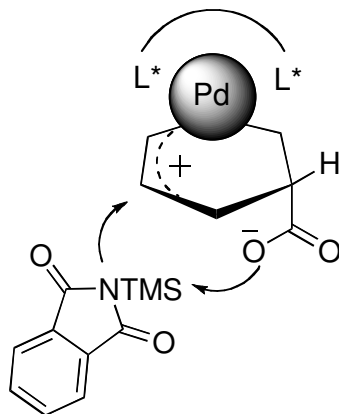


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Shortest Route- Trost



NH(PG)₂ = NHBoc₂, NHCbz₂, NH(CHO)₂, phthalimide



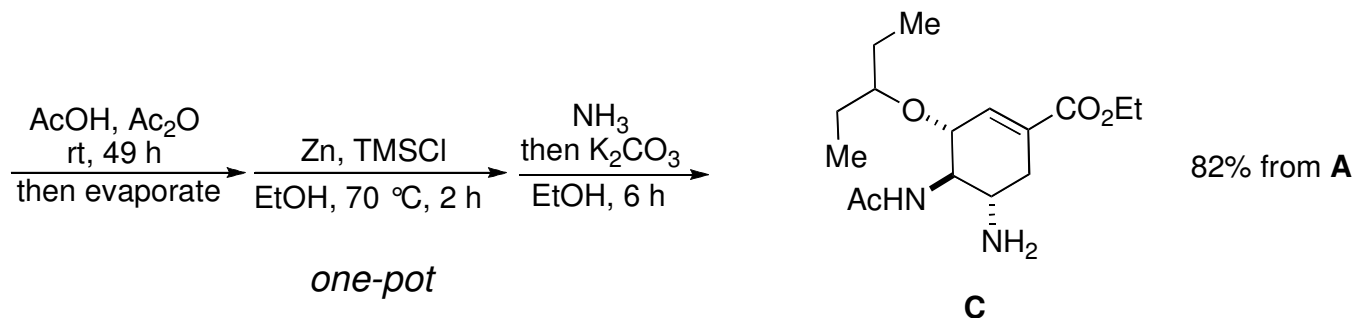
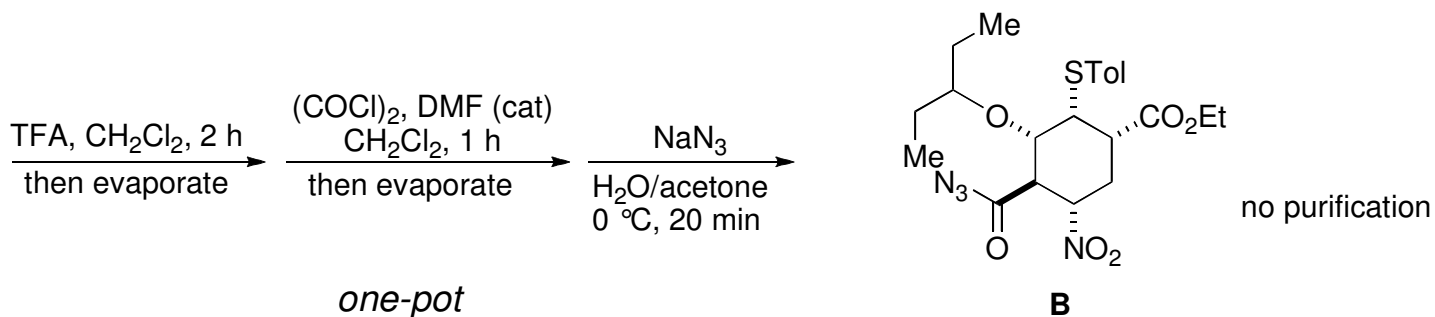
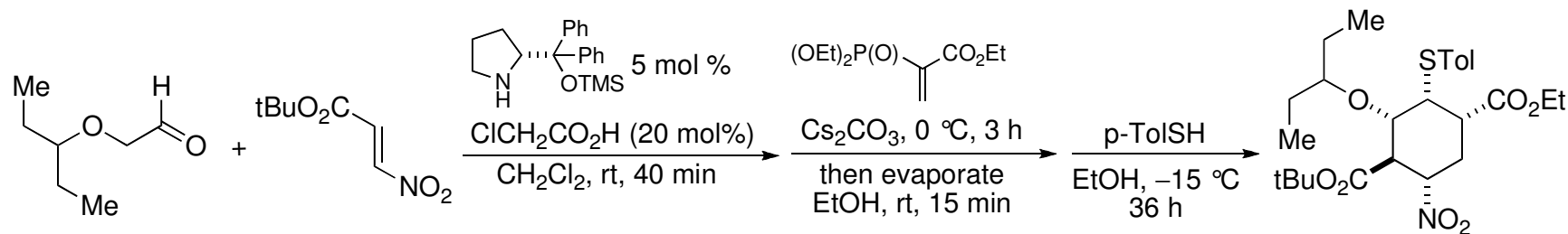
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Shortest Route- Trost

- 30% yield
- 8 steps
- Novel Pd-catalyzed deracemization of lactone
- No azide chemistry

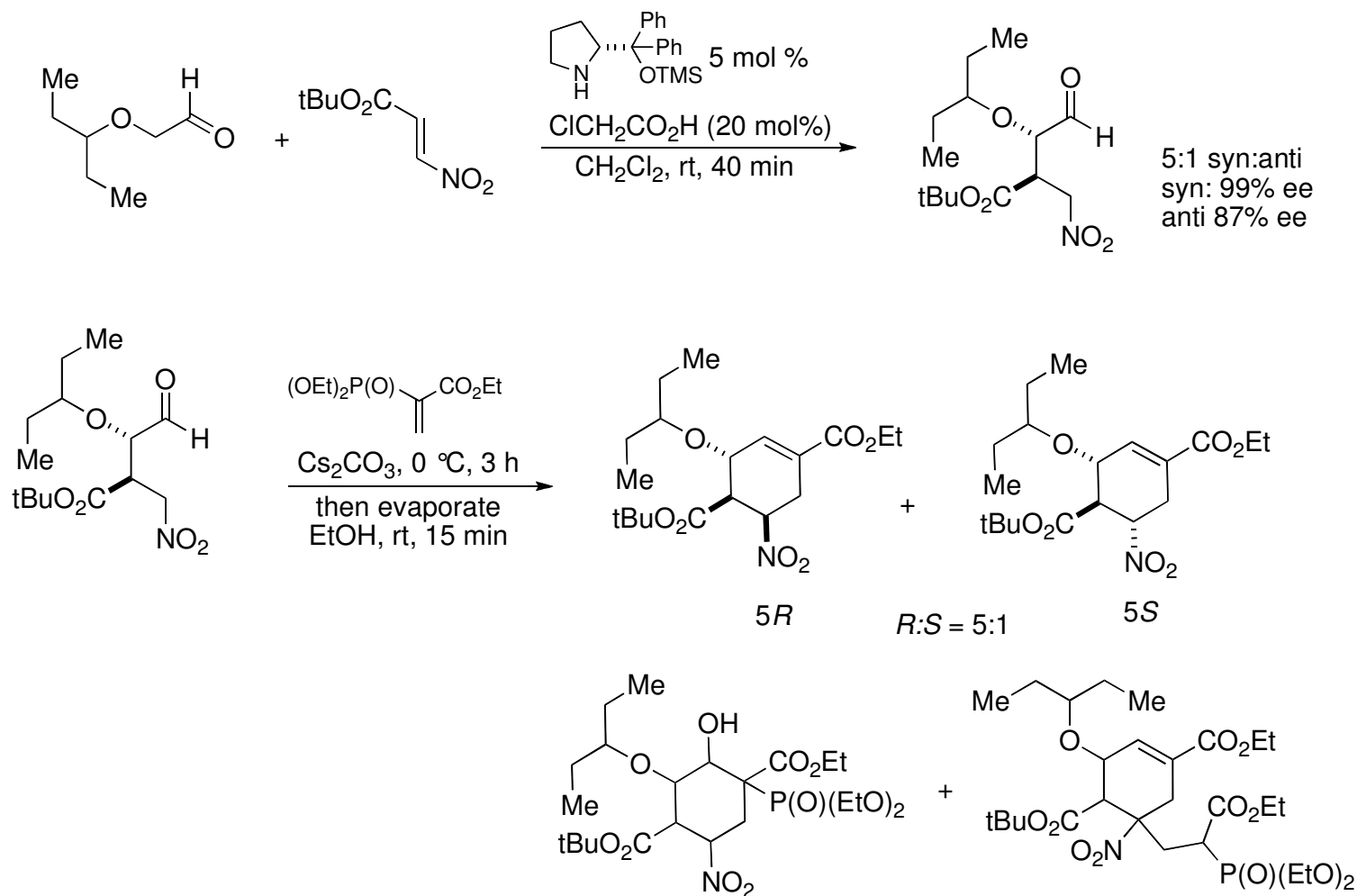
- Microwave
- Hydrazine
- Scale?
- Cost?

Highest Yield- Hayashi



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Highest Yield- Hayashi



Ambrosini 17 - CU Synthesis Lit Group - Tamiflu

Highest Yield- Hayashi

- 57% yield
- 9 steps in 3 reaction pots
- Only one chromatography step
- Inexpensive starting materials

- Uses azide chemistry
- Scale?

Summary

- 1995: Gilead
 - medicinal chemistry route
 - 15% yield in 14 steps
- 2001: Hoffmann-La Roche
 - Optimized route to key epoxide, no azide chemistry
- 2009- Shibasaki
 - New Diels-Alder methodology
 - 16% yield in 12 steps
- 2008- Trost
 - Shortest synthesis: 30% yield in 8 steps
- 2009- Hayashi
 - Highest yield: 57% in 3 reaction pots

References

- Review: J. Magano, *Chem. Rev.* **ASAP**.
- V. Farina, J.D. Brown, *Angew. Chem. Int. Ed.* **2006**, 45, 7330.
- C.U. Kim, et al., *J. Am. Chem. Soc.* **1997**, 119, 681.
- M. Federspiel, et al., *Org. Process Res. Dev.* **1999**, 3, 266.
- M. Karpf, R. Trussardi, *J. Org. Chem.* **2001**, 66, 2044.
- M. Shibasaki, et al., *Angew. Chem. Int. Ed.* **2009**, 48, 1070.
- B.M. Trost, T. Zhang, *Angew. Chem. Int. Ed.* **2008**, 47, 3759.
- H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem. Int. Ed.* **2009**, 48, 1304.