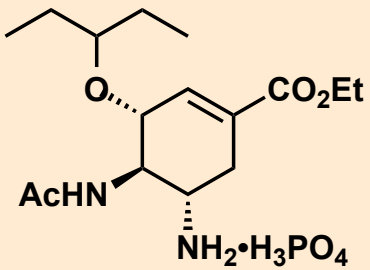
Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)



Oseltamivir phosphate
(Tamiflu)

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2. Industrial synthesis
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Major reference (review): *Eur. J. Org. Chem.,* **2008**, *1839*; *Chem. Rev.,* **2009**, *109,* 4398; *Tetrahedron,* **2011**, *67,* 7875; *Isr. J. Chem.,* **2011**, *51,* 316; *Curr. Org. Chem.,* **2014**, *18,* 2125; *Molecules,* **2016**, *21,* 1513.

Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

1. Introduction

1–1. Background in the development of influenza neuraminidase inhibitors

– Influenza is an RNA virus that is subdivided into three genera: influenza A, B, and C.
– In order for the anti-influenza drug to correspond to high mutation frequency of the influenza virus, the drug needs to be designed to target fundamental molecular processes that are specific for the lifecycle of the virus. For influenza virus, neuraminidase inhibitor (black circle in **Figure**, F) is the prime candidate for broad-spectrum anti-influenza drugs (see **Figure**).

A: Virus linked to the host cell via hemagglutinin, employing terminal of sialic acid (Neu5Ac) residue (yellow) of the surface receptor.
B: Viral RNA released into the cytoplasm, transferred to the hose cell nucleus.
C: Viral RNA replication and mRNA synthesis
D: Viral proteins synthesized, and directed to cell membrane for virus assembly and budding.
E: *Virus surface attached at the sialic acid (Neu5Ac) receptor. Neuraminidase hydrolyze Neu5Ac, allowing the release of the virus.*

F: ***Neuraminidase inhibitor** binding to neuraminidase to prevent releasing virus.*

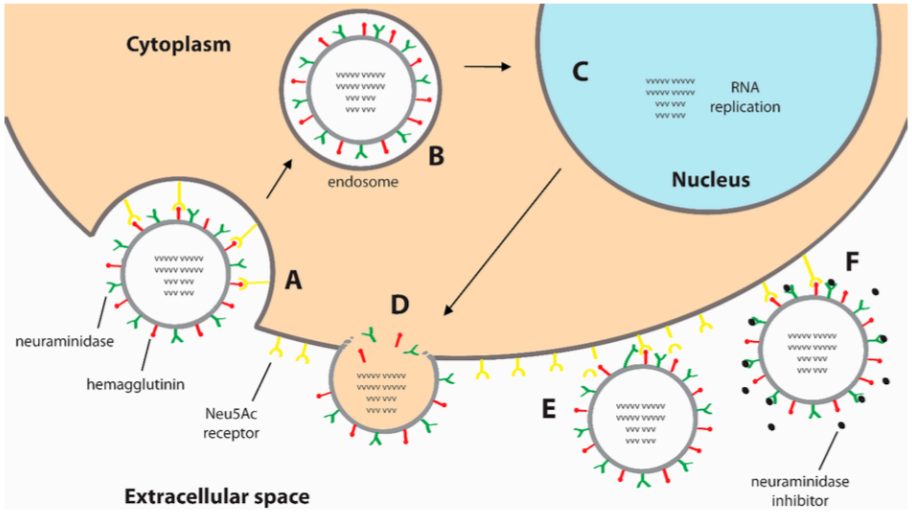
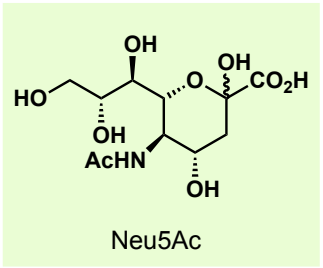
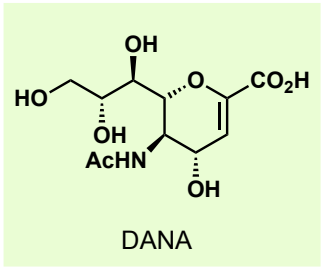


Fig. Influenza virus replication pathway and the effect of neuraminidase inhibitors. (figure copied from *Molecules,* **2016**, *21,* 1513.)

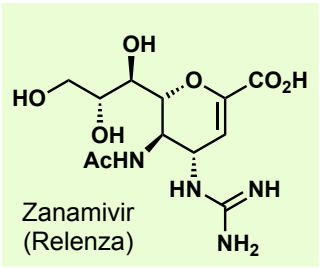
Structures of influenza neuramidase inhibitors



Neu5Ac

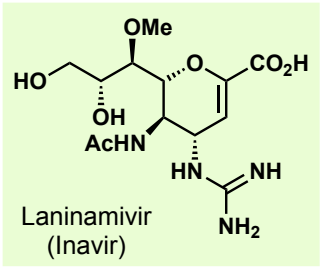


DANA



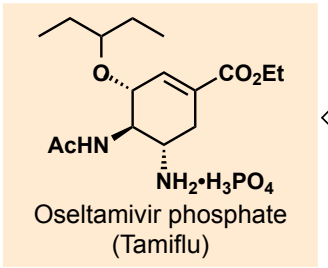
Zanamivir (Relenza)

- Discovered by Biota in 1989
- FDA approved for commercialization in the US in 1999, currently marketed by GlaxoSmithKline.
- Due to poor oral bioavailability (2-3%), it is used as oral inhalation at a dose of 10 mg, twice a day for five days.



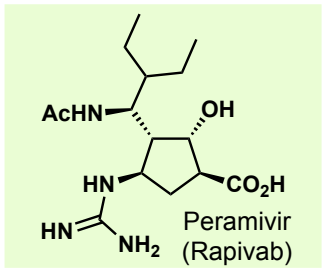
Laninamivir (Inavir)

- Approved for use in Japan in 2010.



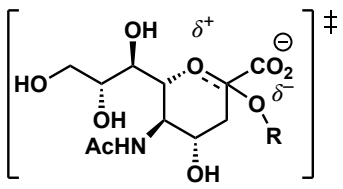
Oseltamivir phosphate (Tamiflu)

see next page



Peramivir (Rapivab)

- Developed by BioCryst Pharmaceticals, FDA approved in 2014.
- Administered intravenously.



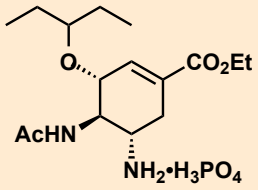
proposed TS during enzymatic hydrolysis of sialylglycosides

- First influenza neuraminidase inhibitor reported in 1974, but never been commercialized.

Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

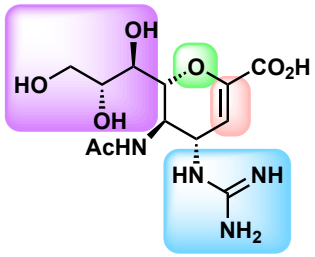
1–2. Tamiflu, analogues, and their bioactivities

main reference: Gilead Sciences, *J. Am. Chem. Soc.*, **1997**, *119*, 681



Oseltamivir phosphate
(Tamiflu)

- Discovered by Gilead Sciences in 1995, and codeveloped with F. Hoffmann-La Roche Ltd.
- FDA approved for commercialization in the US in 1999 as a phosphoric acid salt.
- Used as orally active drug.
- Ethyl ester prodrug is hydrolyzed in the liver by hepatic esterases to the active carboxylate form.



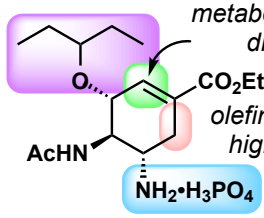
Zanamivir
(Relenza)

modifications

hydrophorbic interaction with neuraminidase (see X-ray)

carbocycle with higher metabolic stability than dihydropyran

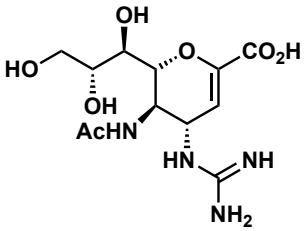
olefin migrated for higher potency



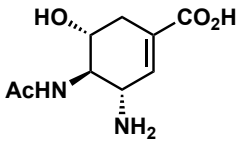
Oseltamivir phosphate
(Tamiflu)

amine•phosphate salt employed for better water-solubility with serum half-life of 3 h

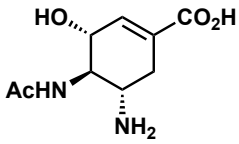
Influenza neuraminidase inhibition by Oseltamivir and its analogues (IC_{50})



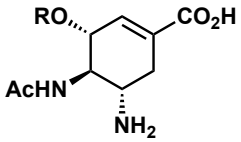
Zanamivir: 1 nM



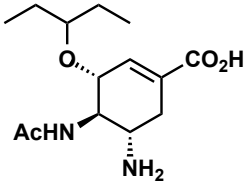
>200,000 nM



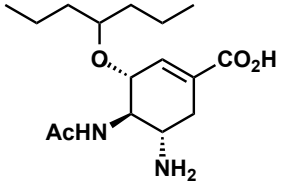
6300 nM



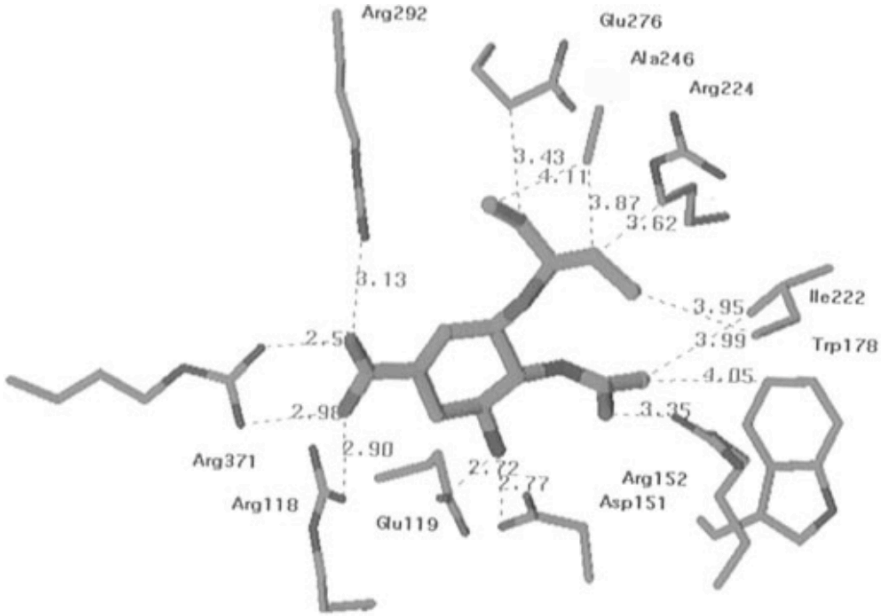
R = Me: 3700 nM
Et: 2000 nM
n-Pr: 180 nM
n-Bu: 300 nM
i-Bu: 200 nM



Oseltamivir: 1 nM



16 nM



X-ray structure of Oseltamivir carboxylate bound to influenza neuraminidase.

Challenges in synthesis:

1. Cheap and readily available starting material.
2. Potential hazards in using toxic and dangerous chemicals (NaN_3, etc.)
3. Less steps and high total yield.
4. Products in almost every step prone to aromatization.

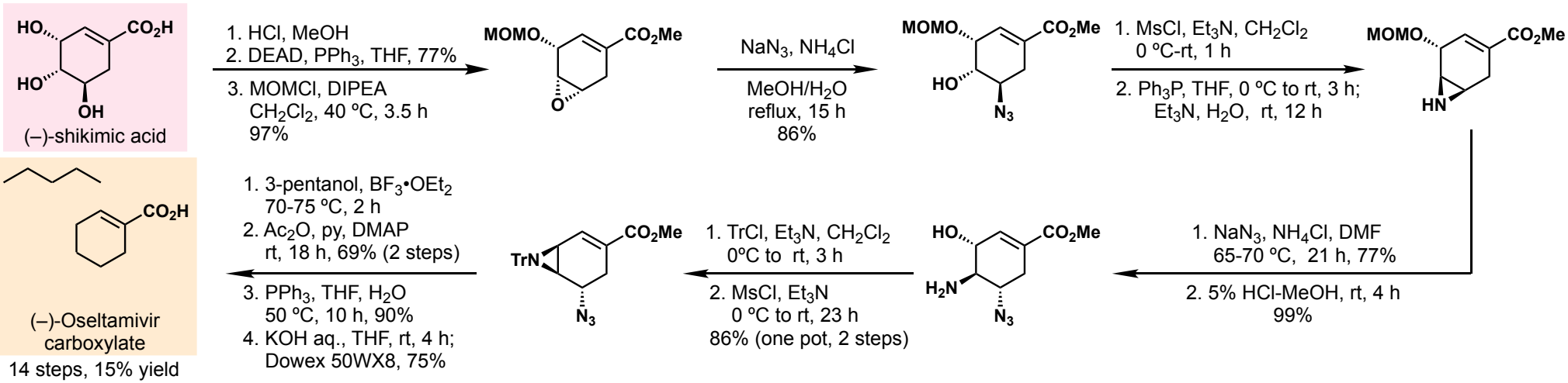
Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

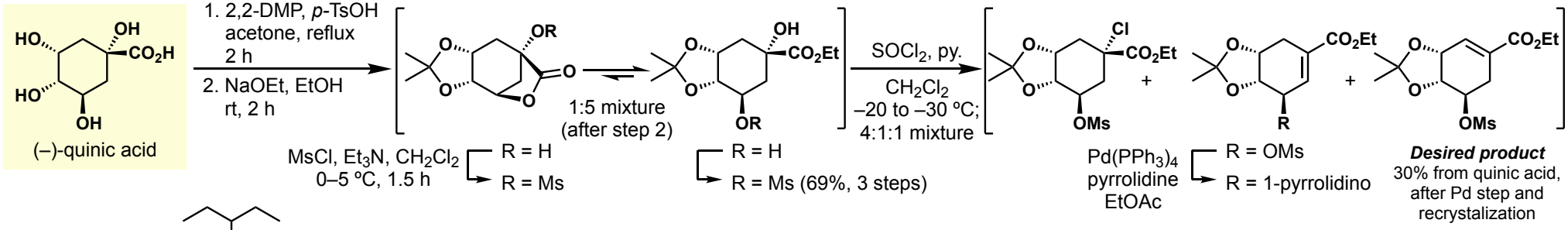
2. Industrial synthesis.

2–1. Gilead Sciences' synthetic route with (–)-shikimic acid and (–)-quinic acid (*J. Am. Chem. Soc.*, **1997**, *119*, 681; *J. Org. Chem.*, **1998**, *63*, 4545)

– First synthesis reported from the medicinal chemistry group at Gilead Scienses using (–)-shikimic acid.

– First large scale synthesis (multi-kg) reported using (–)-quinic acid. (cf. transacetalization was necessary due to lack of crystallinity of 3,4-pentilidine ketal analogues)

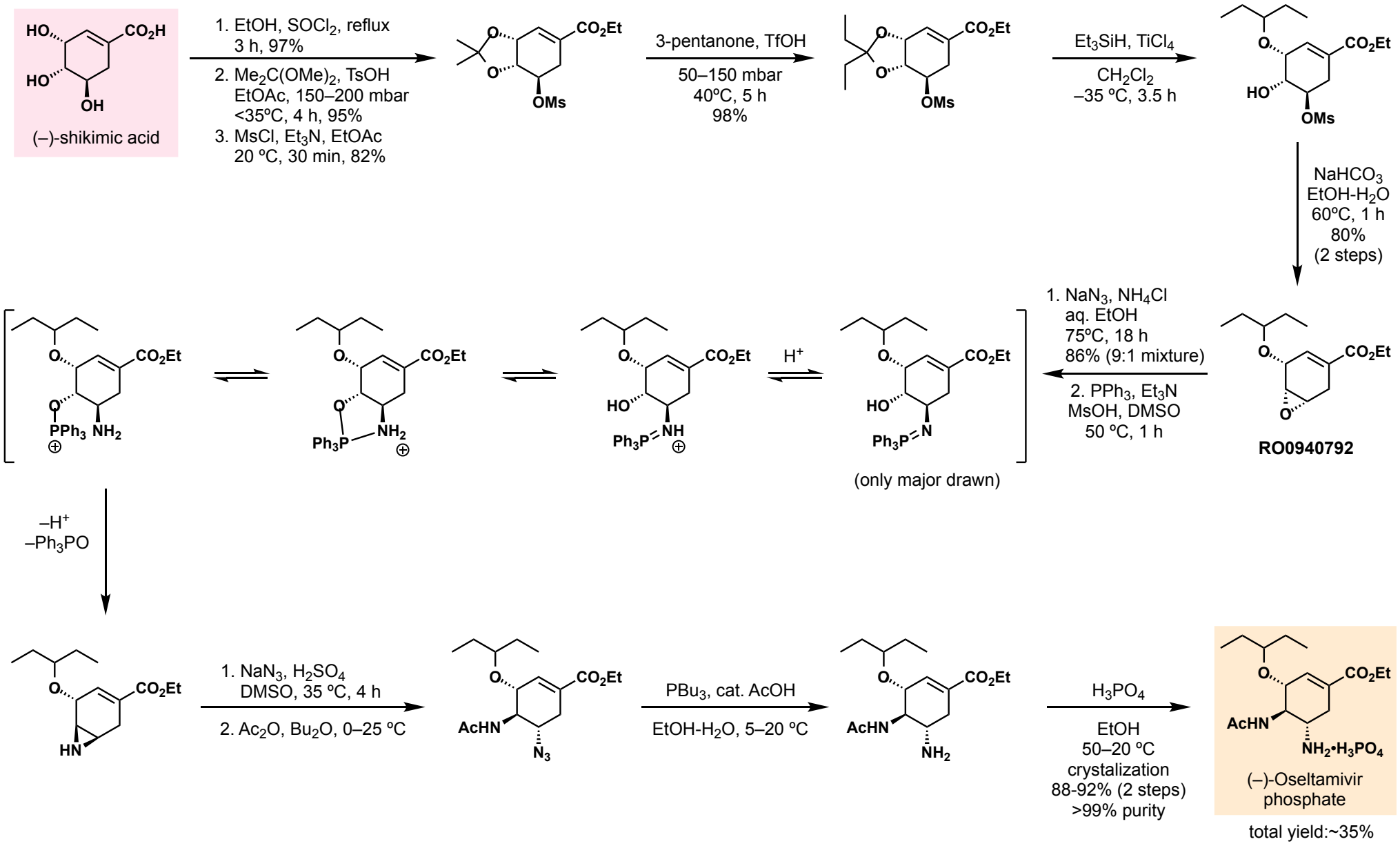




Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

2–2. Roche's process route with (–)-shikimic acid (*Chimia,* **2004**, *58,* 621; **2007**, *61,* 93; and references therein)

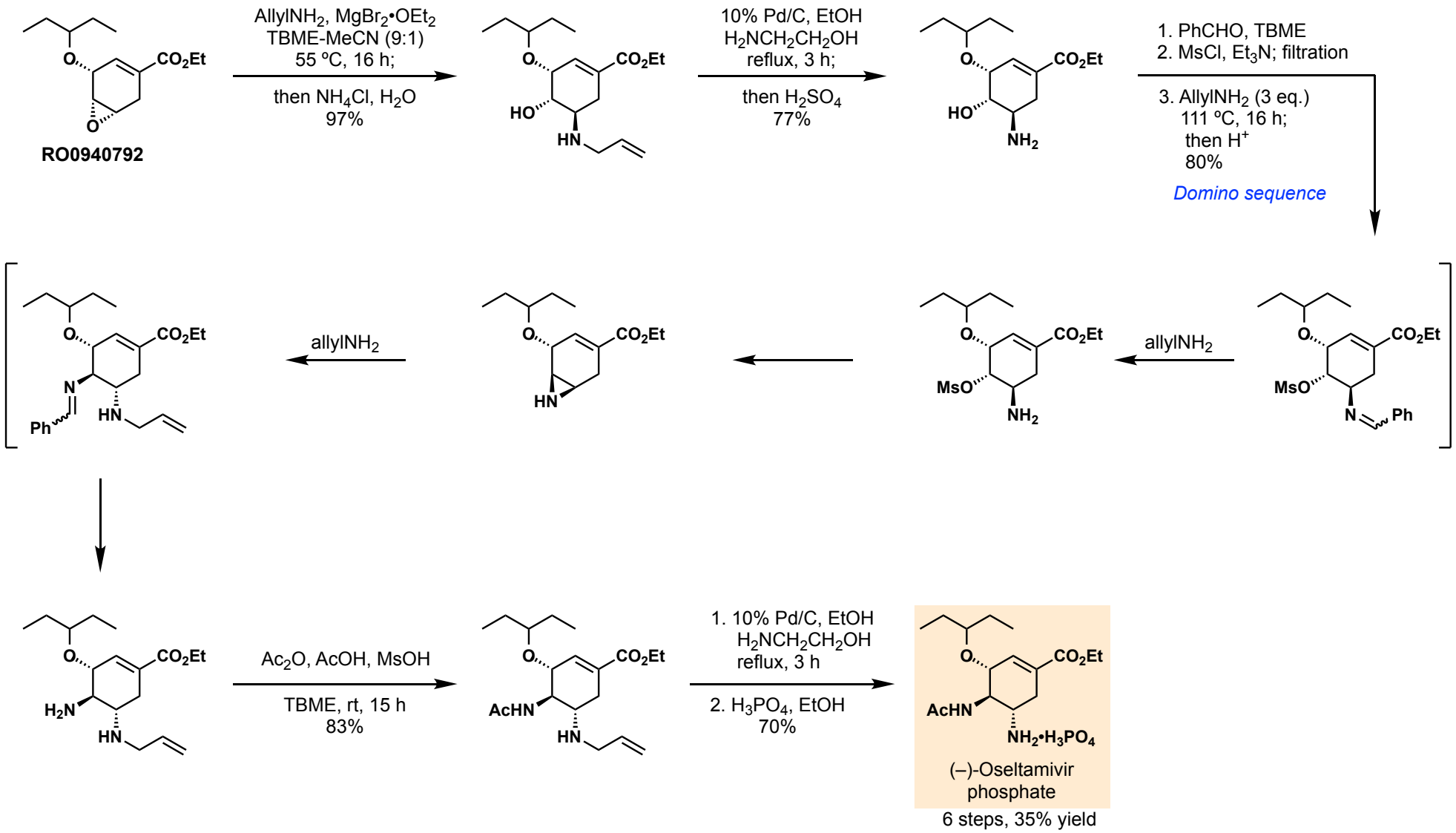
– Ton-scale production route using (–)-shikimic acid.
– (–)-Shikimic acid was chosen as the startming material, instead of (–)-quinic acid, due to better availability by extraction from Chinese star anise (1 kg/30 kg of dried plant) or ferementation using genetigally modified *E. coli*.



Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

2–3. Roche's azide-free route (*Chimia,* **2004**, *58,* 621; **2007**, *61,* 93; and references therein)

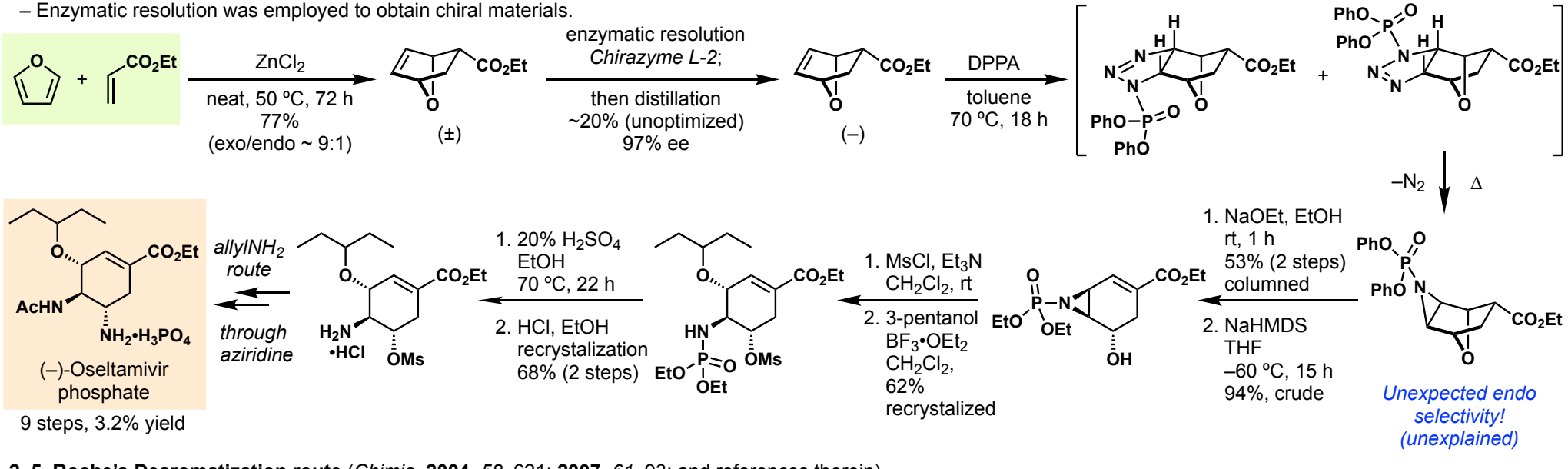
– For search of alternative nitrogen source to replace explosive NaN_3, the use of $BnNH_2$, $\underline{allylNH_2}$, and t-$BuNH_2$ have been examined.



Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

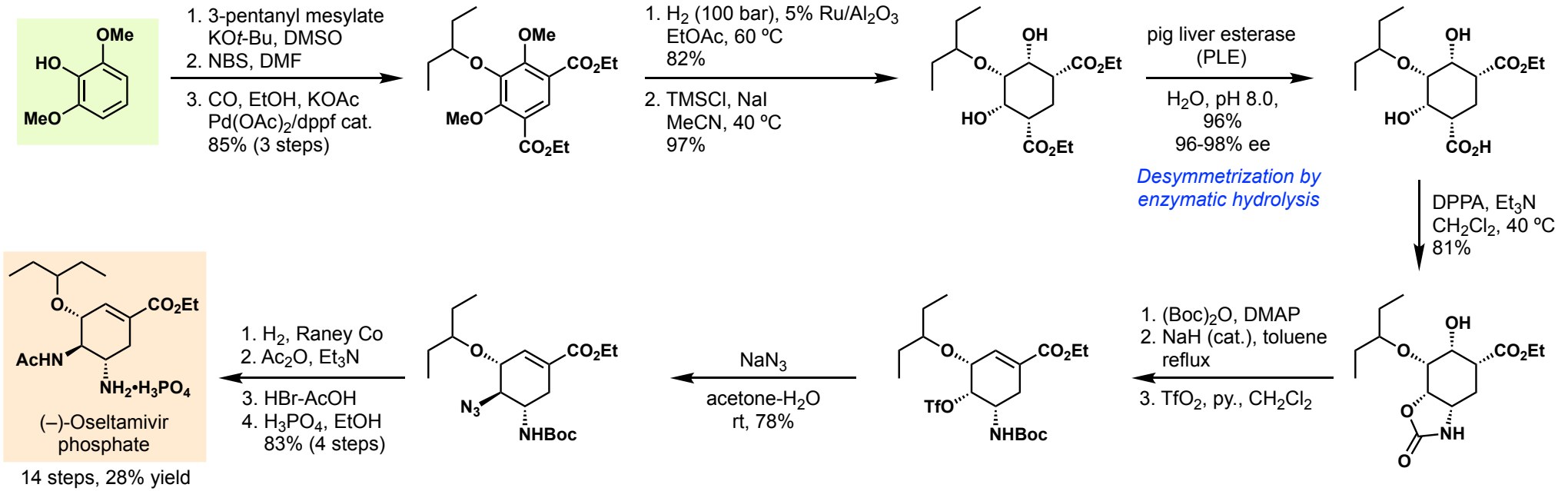
2–4. Roche's Diels-Alder route (*Chimia,* **2004**, *58,* 621; **2007**, *61,* 93; and references therein)

– Developed as a first shikimic acid independent route.
– Enzymatic resolution was employed to obtain chiral materials.



2–5. Roche's Dearomatization route (*Chimia,* **2004**, *58,* 621; **2007**, *61,* 93; and references therein)

– Desymmetrization by enzymatic hydrolysis was employed.

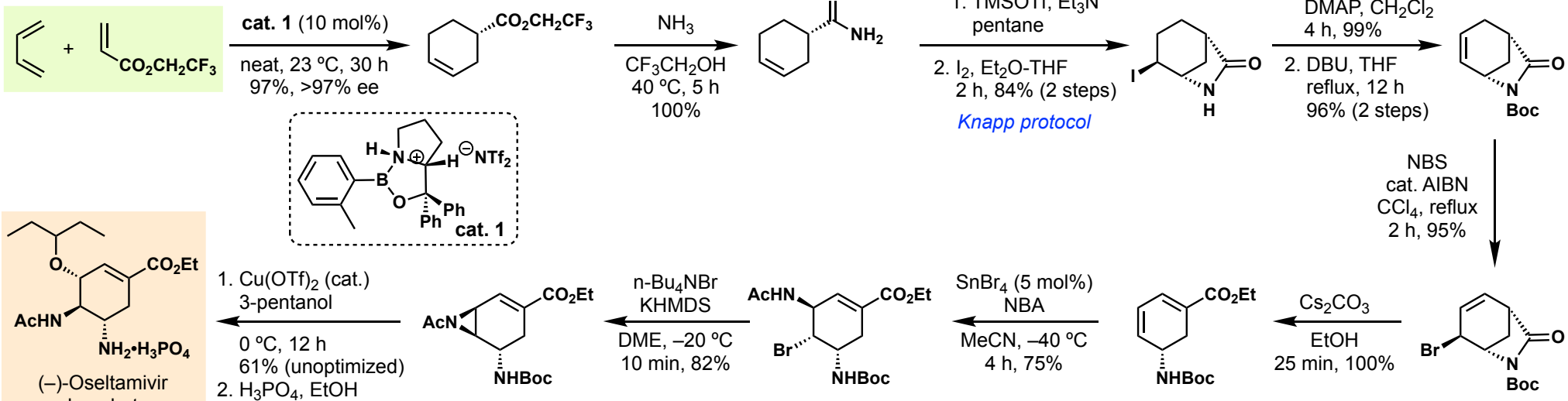


Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

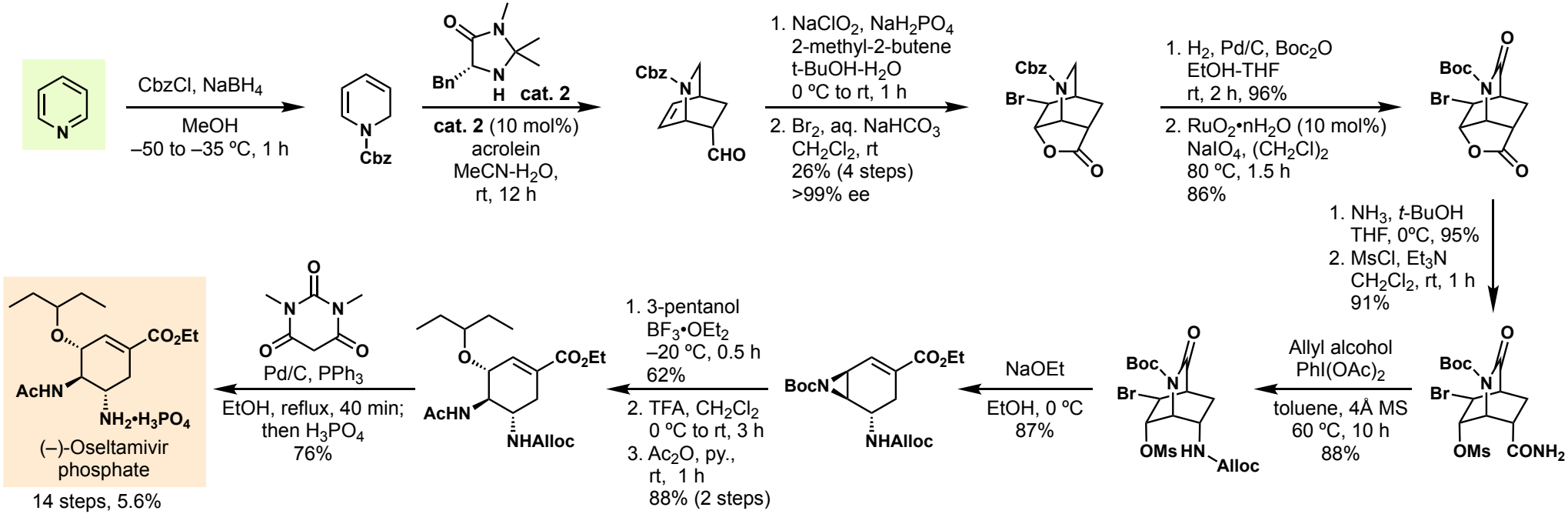
3. Academic synthesis.

3–1. Asymmetric Diels-Alder approaches

3–1–1. Corey's synthesis (*J. Am. Chem. Soc.,* **2006**, *128,* 6310)

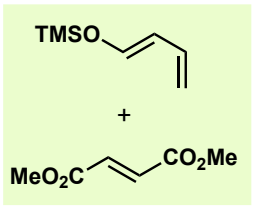


3–1–2. Fukuyama's synthesis (*Angew. Chem. Int. Ed.,* **2007**, *46,* 5734; *Tetrahedron,* **2009**, *65,* 3239)

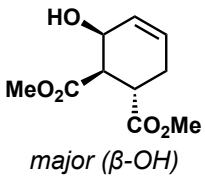


Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

3–1–3. Shibasaki's synthesis: "Fourth generation synthesis" (*Angew. Chem. Int. Ed.,* **2009**, *48,* 1070)

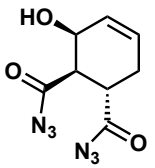


$Ba(O\textit{i}\text{-}Pr)_2$ (2.5 mol%)
ligand 1 (2.5 mol%)
CsF (2.5 mol%)
THF, –20 °C, 36-39 h;
then 1 M aq. HCl
91% α-OH:β-OH=1:5
β-OH: 95% ee

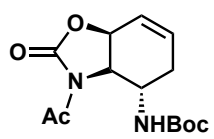


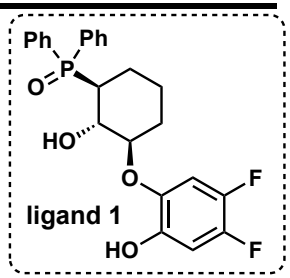
major (β-OH)

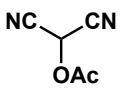
1. NaOH, MeOH
60 °C, 10 h
2. DPPA, Et_3N
THF, 0 °C, 21 h
79% (2 steps)



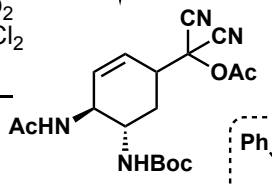
1. *t*-BuOH
80 °C, 13 h
2. Ac_2O, Et_3N
DMAP, CH_2Cl_2
rt, 2.5 h;
then recrystalized
78%, >99% ee



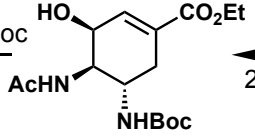




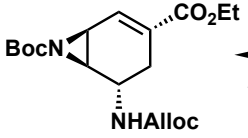
$[Pd_2(dba)_3]\bullet CHCl_3$
(2 mol%)
dppf (4 mol%)
toluene, 60 °C, 30 min
95%



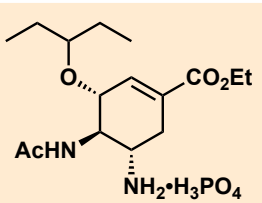
1. TFAA, urea/H_2O_2
Na_2HPO_4, CH_2Cl_2
4 °C, 2 h
2. K_2CO_3, EtOH
rt, 5 h



1. DEAD, PPh_3
p-NO_2PhCO_2H
THF, –20 °C, 1.5 h;
LiOH, EtOH
–20 °C, 15 min
65% (3 steps)
2. DIAD, Me_2PPh
Et_3N, CH_2Cl_2
4 °C, 10 min
83%

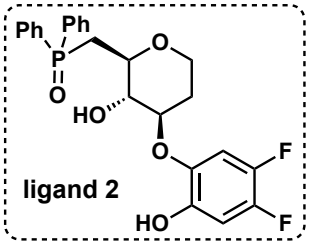


1. $BF_3\bullet OEt_2$
3-pentanol
–20 °C, 15 min
75%
2. TFA; then H_3PO_4
73%



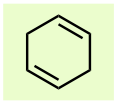
(–)-Oseltamivir phosphate

12 steps, 16% yield



3–2. Asymmetric ring-opening approaches

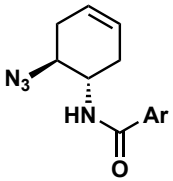
3–2–1. Shibasaki's synthesis: "Second generation synthesis" (*J. Am. Chem. Soc.,* **2006**, *128,* 6312; *Org. Lett.,* **2007**, *9,* 259)



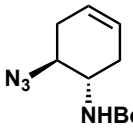
1. *m*CPBA, $NaHCO_3$
CH_2Cl_2, 0 °C to rt, 2 h
2. NaN_3, NH_4Cl
MeOH-H_2O
60 °C, 13 h, 75% (2 steps)
3. PPh_3, MeCN, 60 °C, 2 h
4. 3,5-dinitroBzCl, Et_3N
MeCN, –30 to –10 °C, 1 h
85% (2 steps)

Ar = 3,5-$(NO_2)_2C_6H_3$

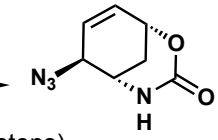
$Y(Oi\text{-}Pr)_3$ (1 mol%)
ligand 2 (2 mol%)
$TMSN_3$
2,6-dimethylphenol
EtCN, rt, 12 h
94%, 89% ee
(99% ee after recrystalization)



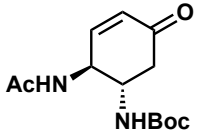
1. $(Boc)_2O$, DMAP
MeCN, rt, 1 h
2. 4 M NaOH
rt, 1 h
98% (2 steps)



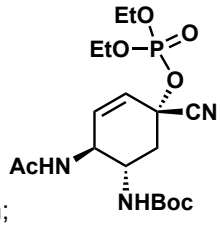
1. I_2, K_2CO_3
KI, $CHCl_3$
60 °C, 15 h
2. DBU, CH_2Cl_2
rt, 4 h, 85% (2 steps)



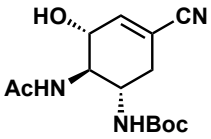
1. $(Boc)_2O$, 99%
2. AcSH, 2,6-lutidine, 83%
3. Cs_2CO_3 (30 mol%), BuOH
4 °C to rt, 16 h, 86%
4. DMP, CH_2Cl_2
4 °C to rt, 15 min, 90%



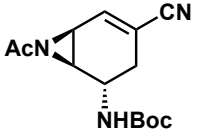
$(EtO)_2P(O)CN$
LiCN
THF
–20 °C, 4 h



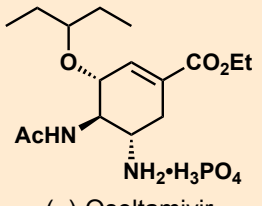
1. toluene
140 °C, 40 min;
aq. NH_4Cl, rt, 3 h
78% (2 steps)
2. DEAD, PPh_3
p-NO_2PhCO_2H
THF, 4 °C, 15 min;
then 1 M aq. LiOH
THF-H_2O, –20 °C, 2.5 h, 80%



DEAD
PPh_3
THF
–20 °C, 2 h
66%



1. $BF_3\bullet OEt_2$
3-pentanol
–20 °C, 5 h
56%
2. HCl, EtOH
rt, 24 h;
H_2O, rt, 7.5 h
60%
3. H_3PO_4, cryst.



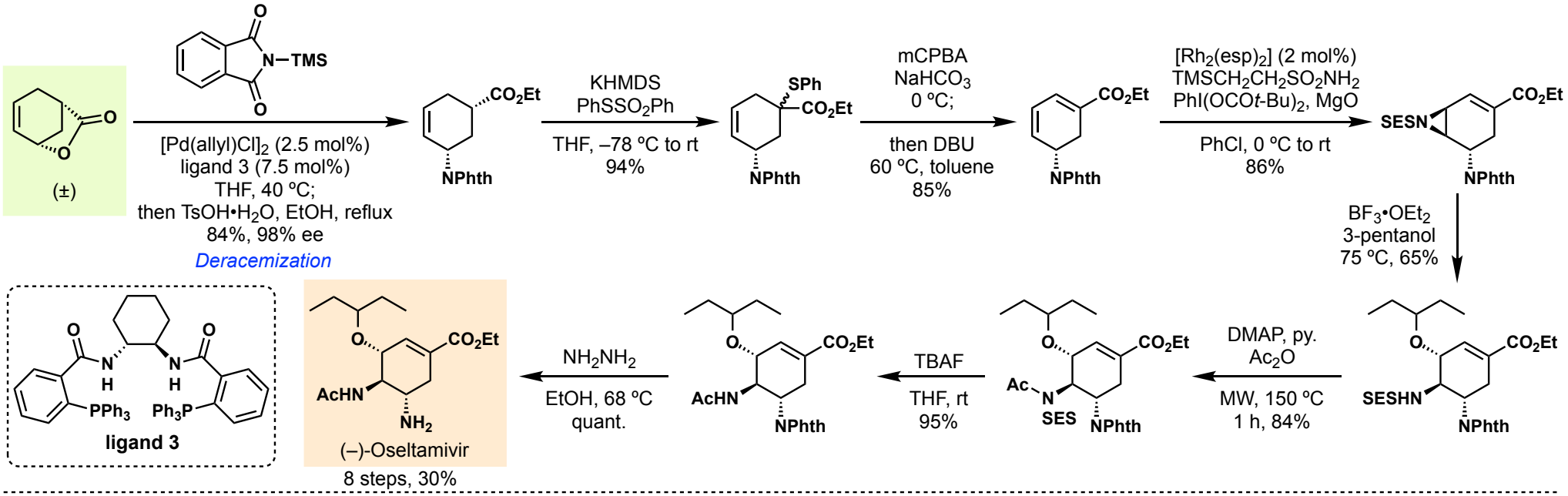
(–)-Oseltamivir phosphate

17 steps, 1.4%

Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

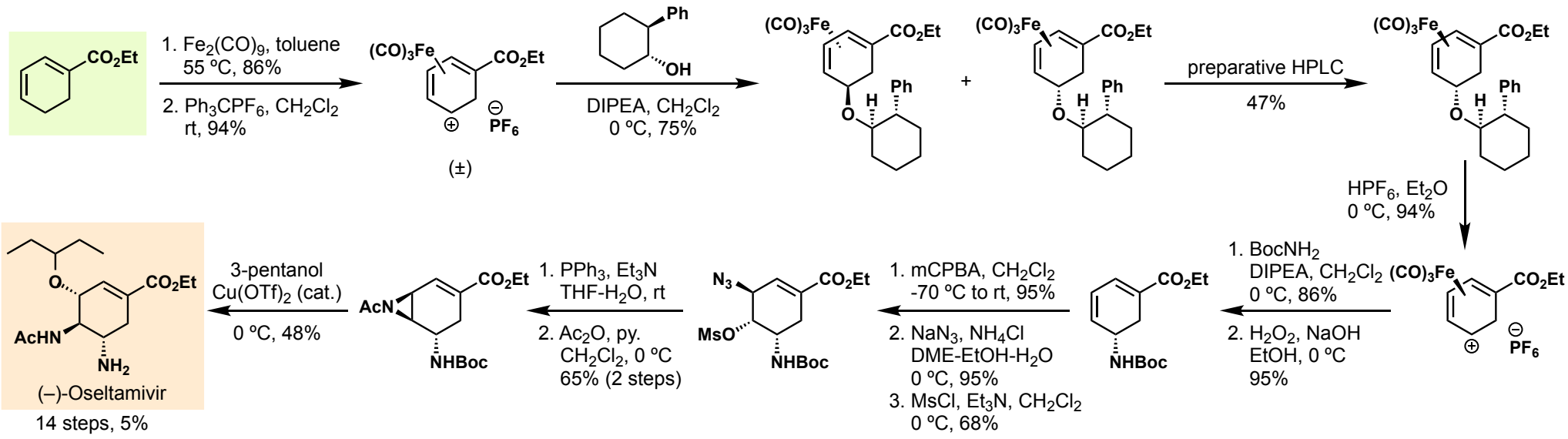
3–3. Asymmetric allylic substitution approaches

3–3–1. Trost's synthesis (*Angew. Chem. Int. Ed.*, **2008**, *47,* 3759; *Chem. Eur. J.*, **2011**, *17,* 3630)



3–4. Iron carbonyl complex approaches

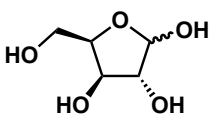
3–4–1. Kann's synthesis (*Chem. Commun.,* **2007**, 3183.)

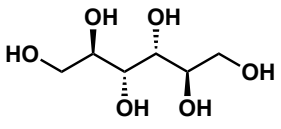


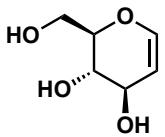
Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

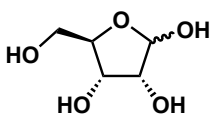
3–5. Chiral sugars as starting materials

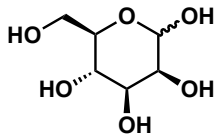
– Sugars that have been employed as the starting material for oseltamivir synthesis:


D-xylose

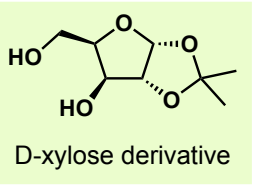

D-mannitol


D-glucal

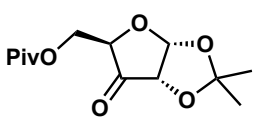

D-ribose


D-mannose

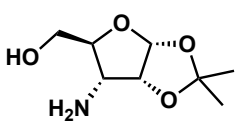
3–5–1. Fang's synthesis (*J. Am. Chem. Soc.,* **2007**, *129,* 11892)


D-xylose derivative

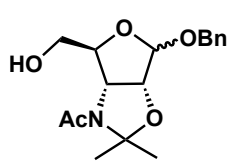
1. *t*-BuCOCl, py. 0 ºC, 8 h, 89%
2. PDC, Ac_2O reflux, 1.5 h



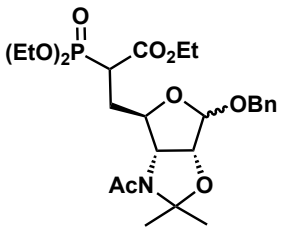
1. $HONH_2$•HCl py., 60 ºC, 24 h 82% (2 steps)
2. LAH, THF 0 ºC to reflux 1.5 h, 88%



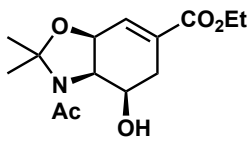
1. Ac_2O, py., 25 ºC, 3 h
2. BnOH, 4 M HCl/dioxane toluene, 0-25 ºC 24 h, 85% (2 steps)
3. $Me_2C(OMe)_2$ cat. TsOH, toluene 80 ºC, 4 h, 90%



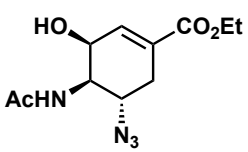
1. Tf_2O, py.. CH_2Cl_2 –15 ºC, 2 h
2. $(EtO)_2P(O)CH_2CO_2Et$ NaH, cat. 15-C-5 DMF, 25 ºC, 24 h 80% (2 steps)



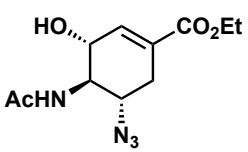
1. H_2, Pd/C, EtOH 25 ºC, 24 h
2. NaH, THF 25 ºC, 1 h 83% (2 steps)



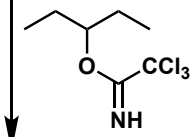
1. DPPA, DIAD PPh_3, THF 25 ºC, 48 h
2. HCl, EtOH reflux, 1 h 83% (2 steps)

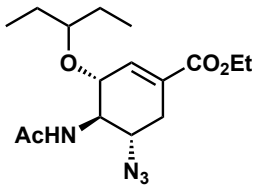


Tf_2O, py., CH_2Cl_2 –15 to –10 ºC, 2 h;
KNO_2, 18-C-6 DMF, 40 ºC, 24 h

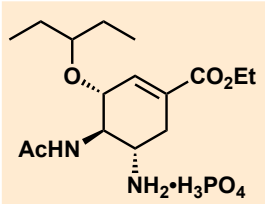


TfOH, CH_2Cl_2 25 ºC, 24 h 78%





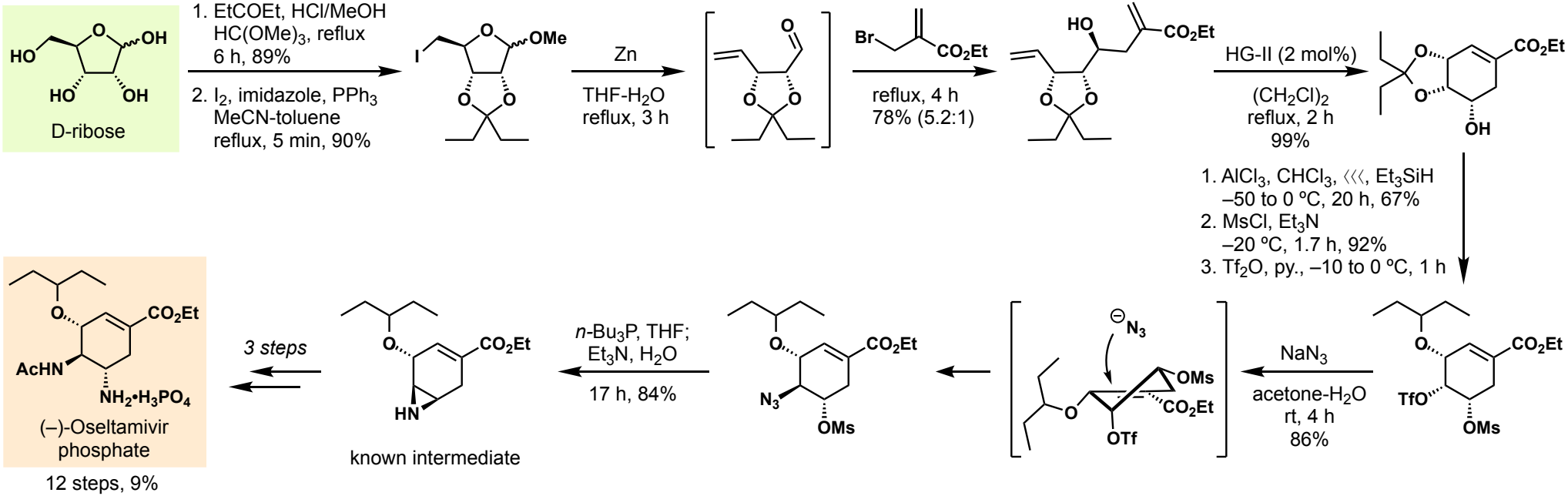
1. H_2, Lindlar cat. EtOH, 25 ºC, 16 h
2. H_3PO_4, EtOH 40 ºC, 1 h 91% (2 steps)


(–)-Oseltamivir phosphate

16 steps, 14%

Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

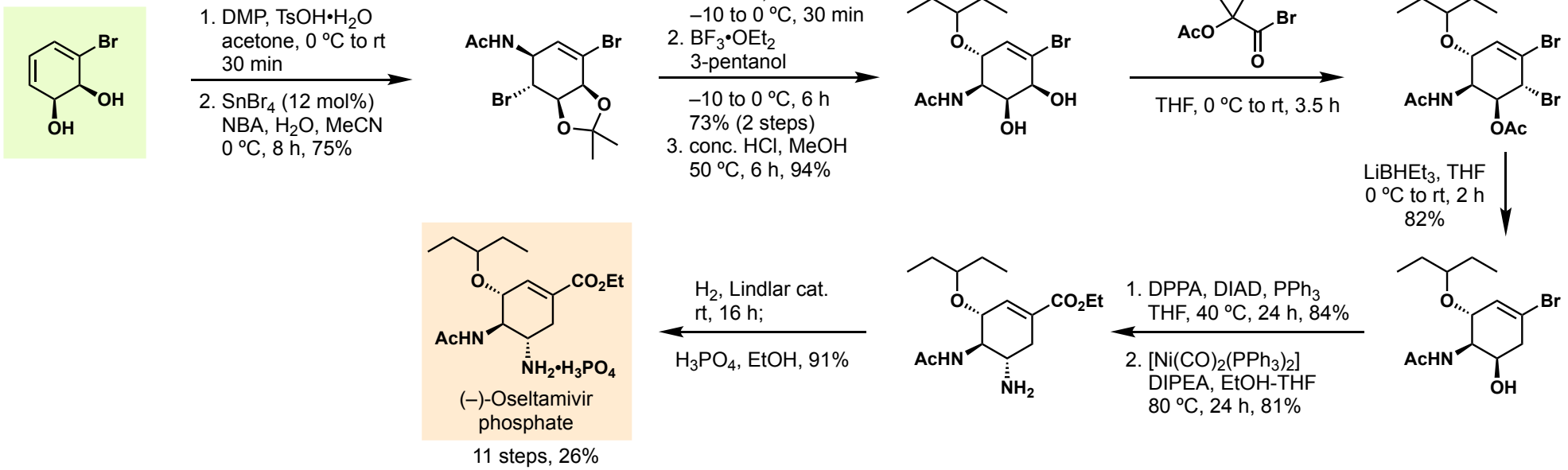
3–5–2. Chen and Chai's synthesis (*Org. Lett.,* **2010**, *12,* 60)



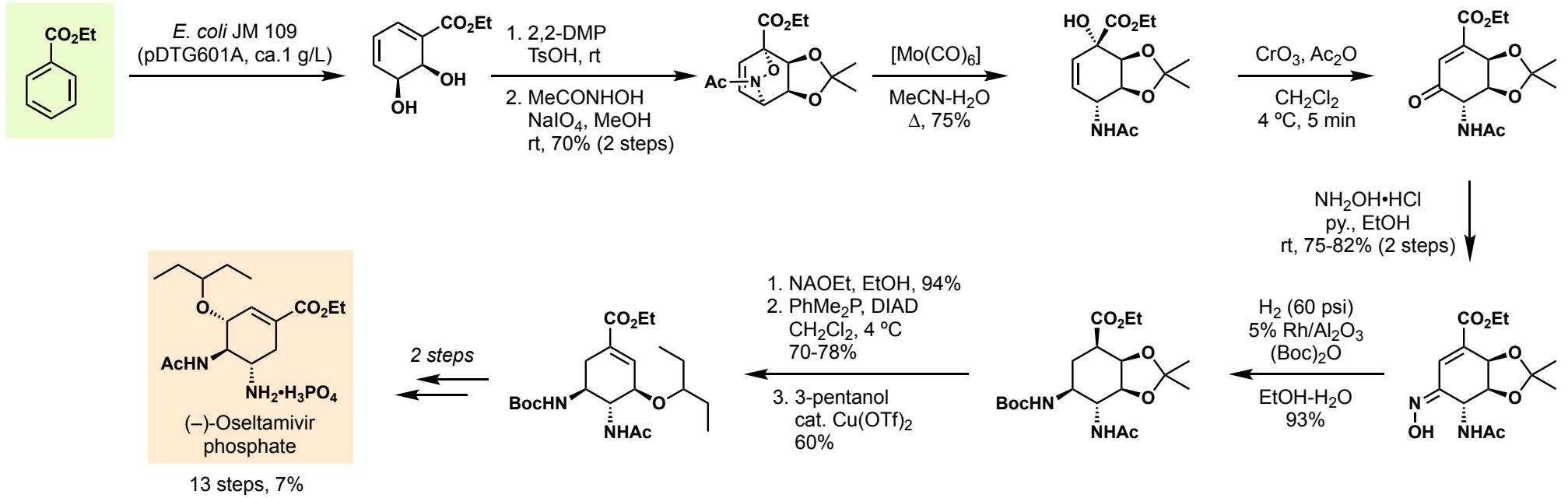
Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

3–6. Chemoenzymatic dearomatization approaches

3–6–1. Fang's synthesis (*Angew. Chem. Int. Ed.,* **2008**, *47*, 5788.)



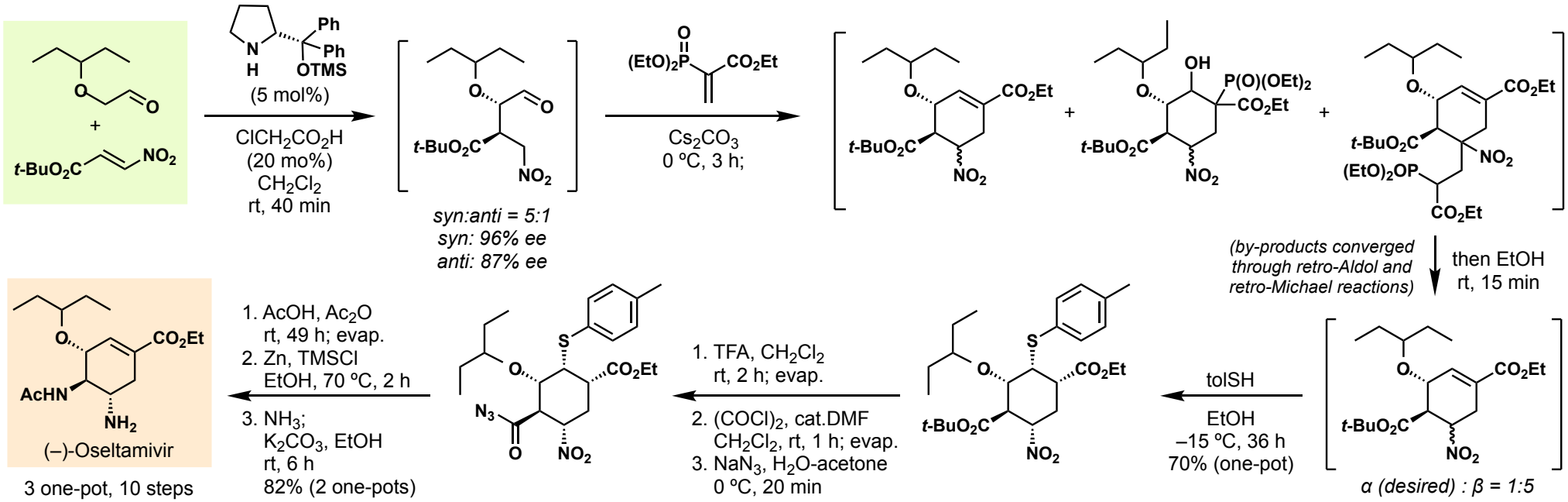
3–6–2. Hudlickey's synthesis (*Angew. Chem. Int. Ed.,* **2009**, *48*, 4229; *Adv. Synth. Catal.,* **2010**, *352*, 195.)

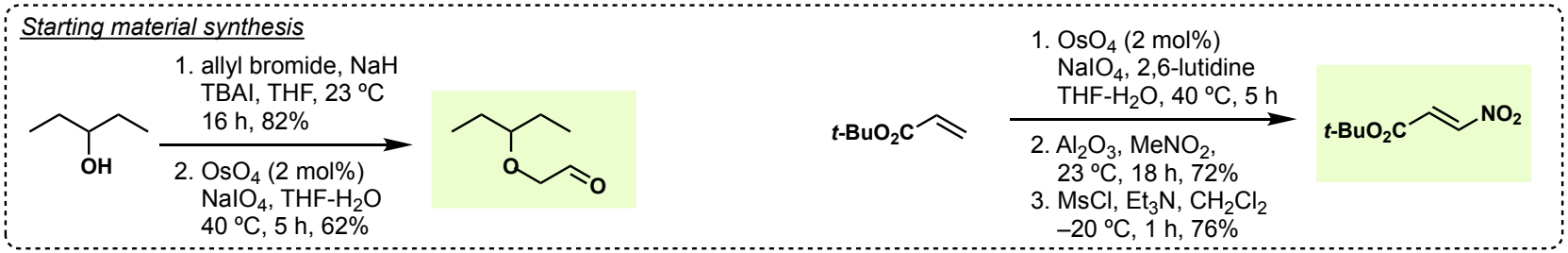


Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

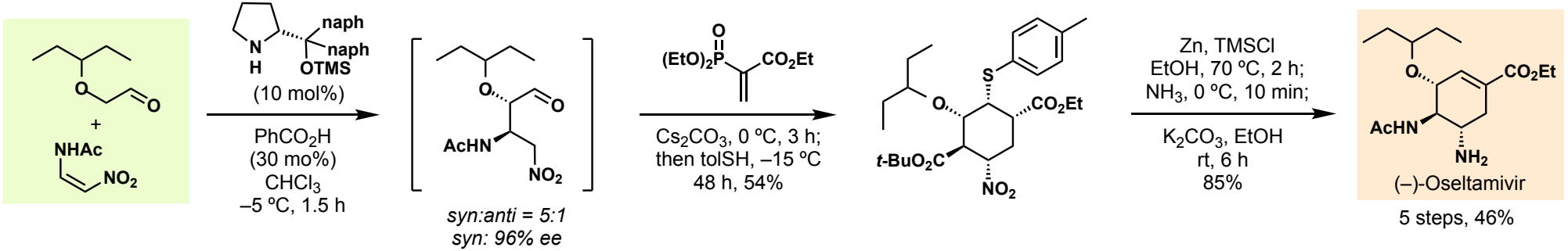
3–7. Asymmetric Michael additions through organocatalysis

3–7–1. Hayasi's "three one-pot" synthesis (*Angew. Chem. Int. Ed.,* **2008**, *47*, 5788.)



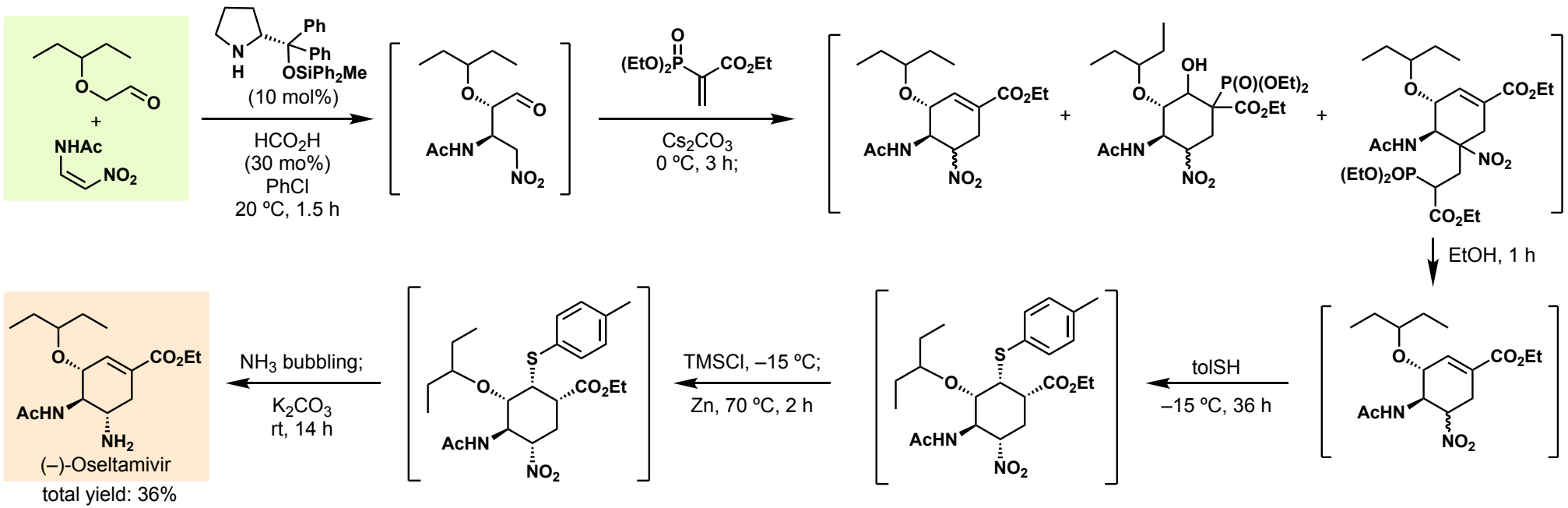


3–7–2. Ma's synthesis (*Angew. Chem. Int. Ed.,* **2010**, *49*, 4656.)



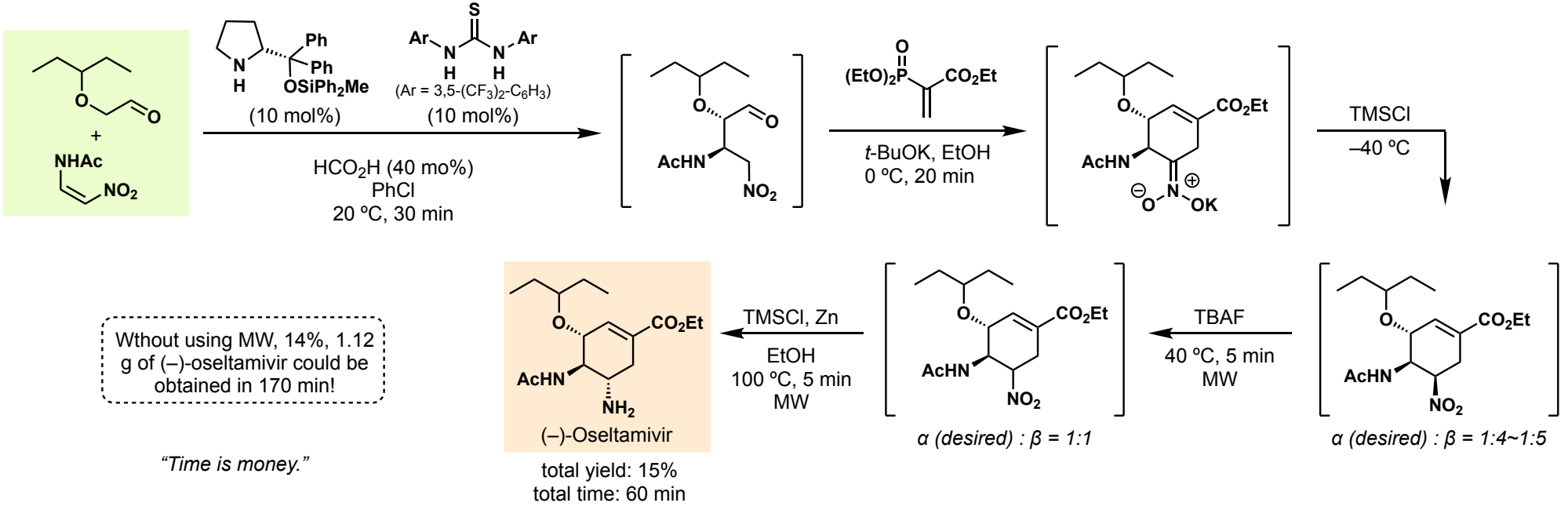
Synthetic Approaches towards Oseltamivir Phosphate (Tamiflu)

3–7–3. Hayasi's "57 h one-pot" synthesis (*Chem. Eur. J.*, **2013**, *19*, 17789.)



total yield: 36%

3–7–4. Hayasi's "60 min one-pot" synthesis (*Org. Lett.*, **2016**, *18*, 3426.)



α (desired) : β = 1:4~1:5

α (desired) : β = 1:1

total yield: 15%
total time: 60 min

Wthout using MW, 14%, 1.12 g of (–)-oseltamivir could be obtained in 170 min!

"Time is money."